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Signed Stephen Hordley

Dated 26 October 2004

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference — 101319-2

29JUL04 E914873-1 D02934
P01/7700 0.00-0416849.8 NONE

2. Patent application number
(The Patent Office will fill in this part) — 0416849.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* — 07822448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

COMPOUNDS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
P O Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* — 08179707001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

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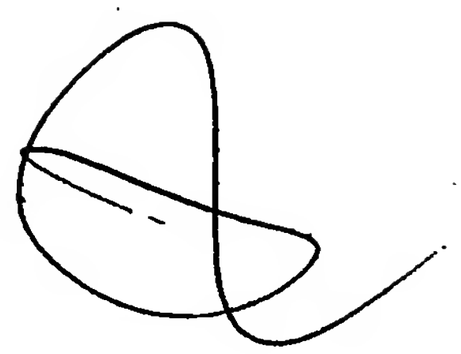
Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	109
Claim *(s)*	6
Abstract	1
Drawing *(s)*	



10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Helen Dixon Date 28.07.200

12. Name and daytime telephone number of person to contact in the United Kingdom — Helen J Dixon 01625 517301

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Compounds

This invention relates to compounds, or pharmaceutically acceptable salts thereof, which possess anti-angiogenic activity and are accordingly useful in methods of treatment of disease states associated with angiogenesis in the animal or human body. The invention also concerns processes for the preparation of the compounds, pharmaceutical compositions containing the compounds as active ingredient, and methods for the use of the compounds in the manufacture of medicaments for use in the production of anti-angiogenic effects in warm-blooded animals such as humans.

The Tie2 receptor tyrosine kinase (also known as TEK) is expressed predominantly in endothelial and haematopoietic cells and is essential for vessel formation and maintenance (Jones, N. et al. Nature Reviews Molecular Cell Biology. 2001: 2, 257-67).

Angiogenesis is a fundamental process defined as the generation of new blood vessels from existing vasculature. It is a vital yet complex biological process required for the formation and physiological functions of virtually all the organs. Normally it is transient in nature and is controlled by the local balance of angiogenic and angiostatic factors in a multi-step process involving vessel sprouting, branching and tubule formation by endothelial cells (involving processes such as activation of endothelial cells (ECs), vessel destabilisation, synthesis and release of degradative enzymes, EC migration, EC proliferation, EC organisation and differentiation and vessel maturation).

Normal angiogenesis plays an important role in a variety of processes and is under stringent control. In the adult, physiological angiogenesis is largely confined to wound healing and several components of female reproductive function and embryonic development. In undesirable or pathological angiogenesis, the local balance between angiogenic and angiostatic factors is dysregulated leading to inappropriate and/or structurally abnormal blood vessel formation. Pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacology. Science. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). In cancer, growth of primary and secondary tumours beyond 1-2 mm^3 requires angiogenesis (Folkman, J. New England Journal of Medicine 1995; 33, 1757-1763).

In diseases such as cancer in which progression is dependant on aberrant angiogenesis, blocking the process can lead to prevention of disease advancement (Folkman, J. 1995, Nature

Medicine. 1: 27-31). Many factors are described in the scientific literature that are believed to play important critical roles in the regulation of angiogenesis. Two major classes of angiogenic factors are the vascular endothelial growth factor (VEGF) and the angiopoietins. These polypeptide moieties interact with their respective receptors (transmembrane tyrosine kinases which are predominantly endothelial cell specific) and induce cellular responses via ligand mediated signal transduction. It has been speculated that VEGF and the angiopoietins co-operate to regulate various aspects of the angiogenic process during both normal and pathological angiogenesis via signalling through their respective receptors.

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity that leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt or Flt1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another fms-like tyrosine kinase receptor, Flt4. Two of these related RTKs, Flt and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

Recently a second family of predominantly endothelial cell specific receptors that regulate vessel destabilisation and maturation have been identified. The Tie receptors and their ligands, the angiopoietins, co-operate closely with VEGF during both normal and pathological angiogenesis. The transmembrane receptors Tie1 and Tie2, constitute a family of endothelial cell specific tyrosine kinase receptors involved in maintenance of blood vessel integrity and which are involved in angiogenic outgrowth and vessel remodelling. Structurally Tie1 and Tie2 share a number of features (e.g. the intracellular domains of both these receptors each contain a tyrosine kinase domain interrupted by a kinase insert region) and thus constitute a distinct RTK subfamily. Overall sequence identity between Tie1 and

Tie2 receptors at the amino acid level is 44% while their intracellular domains exhibit 76% homology. Targeted disruption of the Tie1 gene results in a lethal phenotype characterised by extensive haemorrhage and poor microvessel integrity (Puri, M. et al. 1995 EMBO Journal: 14:5884-5891). Transgenic mice deficient in Tie2 display defects in vessel sprouting and remodelling and display a lethal phenotype in mid gestation (E9.5-10.5) caused by severe defects in embryonic vasculature (Sato, T. et al. 1995 Nature 370: 70-74).

To date no ligands have been identified for Tie1 and little is known regarding its signalling abilities. However, Tie1 is believed to influence Tie2 signalling via heterodimerisation with the Tie2 receptor, hence potentially modulating the ability of Tie2 to autophosphorylate (Marron, M. et al. 2000 Journal of Biological Chemistry: 275, 39741-39746) and recent chimaeric Tie1 receptor studies have indicated that Tie-1 may inhibit apoptosis via the PI 3 kinase/Akt signal transduction pathway (Kontos, C.D., et al., 2002 Molecular and Cellular Biology: 22, 1704-1713). In contrast, a number of ligands, designated the angiopoietins have been identified for Tie2 of which Angiopoietin 1 (Ang1) is the best characterised. Binding of Ang1 induces tyrosine phosphorylation of the Tie2 receptor via autophosphorylation and subsequently activation of its signalling pathways via signal transduction. Ang2 has been reported to antagonise these effects in endothelial cells (Maisonpierre, P. et al. 1997 Science: 277, 55-60). The knock-out and transgenic manipulation of Tie2 and its ligands suggest that stringent spatial and temporal control of Tie2 signalling is imperative for the correct development of new vasculature. There are also reports of at least another two ligands (Ang3 and Ang4) as well as the possibility of heterodimerisation between the angiopoietin ligands that has the potential to modify their activity (agonistic/antagonistic) on association with the receptor. Activation of the Tie2 receptor by Ang1 inhibits apoptosis (Papapetropoulos, A., et al., 2000 Journal of Biological Chemistry: 275 9102-9105), promotes sprouting in vascular endothelial cells (Witzenbicher, B., et al., 1998 Journal of Biological Chemistry: 273, 18514-18521) and *in vivo* promotes blood vessel maturation during angiogenesis and reduces the permeability and consequent leakage from adult microvessels (Thurston, G. et al., 2000 Nature Medicine: 6, 460-463). Thus activated Tie2 receptor is reported to be involved in the branching, sprouting and outgrowth of new vessels and recruitment and interaction of periendothelial support cells important in maintaining vessel integrity and overall appears to be consistent with promoting microvessel stability. Absence of Tie2 activation or inhibition of Tie2 auto phosphorylation may lead to a loss of vascular structure and matrix/cell contacts (Thurston, G., Cell Tissue

Res (2003), 314: 61-69) and in turn may trigger endothelial cell death, especially in the absence of survival or growth stimuli. On the basis of the above reported effects due to Tie2 kinase activity, inhibiting Tie2 kinase may provide an anti-angiogenic effect and thus have application in the therapy of disease states associated with pathological angiogenesis. Tie2 expression has been shown to be up-regulated in the neovasculature of a variety of tumours (e.g. Peters, K.G. et al, (British Journal of Cancer, 1998; 77,51-56) suggesting that inhibiting Tie2 kinase activity will result in anti-angiogenic activity. In support of this hypothesis, studies with soluble Tie2 receptor (extracellular domain) (Pengnian, L. et al., 1997, Journal of Clinical Investigation 1997: 100, 2072-2078 and Pengnian, L. et al., 1998, Proceedings of the National Academy of Sciences 1998: 95, 8829-8834) have shown anti-tumour activity in *in vivo* tumour models. In addition these experiments also indicate that disruption of the Tie2 signalling pathways in a normal healthy individual may be well tolerated as no adverse toxicities were observed in these studies.

Examination of human primary breast cancer samples and human and murine breast cancer cell lines (Stratmann, A., et al., 2001, International Journal of Cancer: 91, 273-282) indicate that Tie2 dependant pathways of tumour angiogenesis may exist alongside KDR dependant pathways and, in fact, may operate both independently (Siemeister G., et al., 1999 Cancer Research: 59, 3185-3191) as well as in concert with each other (e.g. VEGF A and Ang1 reported to collaborate to induce angiogenesis and produce non-leaky mature vessels Thurston, G, et al., 1999 Science: 286, 2511-2514). It is quite possible that a mix of such angiogenic processes even exist within a single tumour.

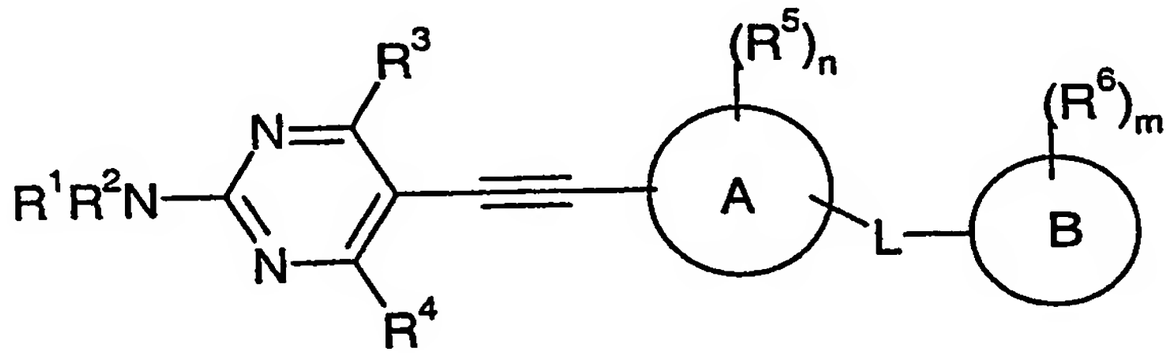
Tie2 has also been shown to play a role in the vascular abnormality called venous malformation (VM) (Mulliken, J.B. & Young, A.E. 1998, Vascular Birthmarks: W. B. Saunders, Philadelphia). Such defects can either be inherited or can arise sporadically. VM's are commonly found in the skin or mucosal membranes but can affect any organ. Typically lesions appear as spongy, blue to purple vascular masses composed of numerous dilated vascular channels lined by endothelial cells. Among the inherited forms of this disease the most common defect appears to be a Tie2 kinase mutation C2545T in the Tie2 coding sequence (Calvert, J.T., et al., 1999 Human Molecular genetics: 8, 1279-1289), which produces a R849W amino acid substitution in the kinase domain. Analysis of this Tie2 mutant indicates that it is constitutively activated even in the absence of ligand (Vikkula, M., et al., 1996 Cell: 87, 1181-1190).

Upregulation of Tie2 expression has also been found within the vascular synovial pannus of arthritic joints in humans, which is consistent with the role of inappropriate neovascularisation.

Such examples provide further indications that inhibition of Tie2 phosphorylation and subsequent signal transduction will be useful in treating disorders and other occurrences of inappropriate neovascularisation. To date only a few inhibitors of Tie2 are known in the art. There is thus a need to identify additional Tie2 inhibitors that could exploit the full therapeutic potential of inhibiting/ modulating the Tie2 signalling pathways.

We have found that certain compounds possess inhibitory activity for the Tie2 receptor tyrosine kinase and accordingly have value in the treatment of disease states associated with pathological angiogenesis such as cancer, rheumatoid arthritis, and other diseases where active angiogenesis is undesirable.

According to a first aspect of the present invention there is provided a compound of the Formula I:



Formula I

wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group $–N(R^d)CO$(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring, or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy,

(1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups independently selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or $-C(O)(CH_2)_zY$ wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy,

wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of **R^3** and **R^4** is as defined above and the other represents a group **$-NR^1R^2$** as defined above;

A represents an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl,

thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^5 is selected from cyclopropyl, cyano, halo, (1-6C)alkoxy or (1-6C)alkyl, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L is attached meta or para on ring A with respect to the point of attachment of the ethynyl group and represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)-NR^9, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -$N(R^c)$CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3;

and when B is a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a saturated or partially saturated 8, 9 or 10 membered bicyclic group, the rings and the bicyclic group optionally bear 1 or 2 oxo or thioxo substituents;

and pharmaceutically acceptable salts thereof.

According to another aspect of the present invention there is provided a compound of the Formula I wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group $–N(R^d)CO$(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring, or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups independently selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a

saturated or partially saturated 3 to 7 membered heterocyclic ring or -C(O)$(CH_2)_z$Y wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy,

wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

A represents an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^5 is selected from cyclopropyl, cyano, halo, (1-6C)alkoxy or (1-6C)alkyl, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L is attached meta or para on ring A with respect to the point of attachment of the ethynyl group and represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)-NR^9, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group $-N(R^c)CO(1\text{-}6C)alkyl$ in which R^c is H or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3;

and when B is a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a saturated or partially saturated 8, 9 or 10 membered bicyclic group, the rings and the bicyclic group optionally bear 1 or 2 oxo or thioxo substituents;
and pharmaceutically acceptable salts thereof.

According to another aspect of the present invention there is provided a compound of the Formula I wherein:

R^1 **and** R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, or (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or R^1 **and** R^2 together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the alkyl and the cycloalkyl groups are optionally substituted by one or more groups selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and wherein the phenyl is optionally substituted by one or more groups selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl or (1-6C)alkoxy are optionally substituted by hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring; or one of R^3 and R^4 is as defined above and the other represents a group $-NR^1R^2$ as defined above;

A represents an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^5 is selected from cyano, halo, (1-6C)alkoxy or (1-6C)alkyl optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L is attached meta or para on ring A with respect to the point of attachment of the ethynyl group and represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)- NR^9 wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl ;

B represents a (3-7C)cycloalkyl ring, an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^6 is selected from halo, cyano, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -$N(R^c)$CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3; and when m is at least 2 then two substituents on adjacent carbon atoms in ring B may together represent a methylenedioxy group;
and pharmaceutically acceptable salts thereof.

According to another aspect of the present invention there is provided a compound of the Formula I wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, or (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the alkyl and the cycloalkyl groups are optionally substituted by one or more groups selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered

heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and the phenyl is optionally substituted by one or more groups selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl or (1-6C)alkoxy are optionally substituted by hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

A represents an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^5 is selected from (1-6C)alkoxy, cyano, halo or (1-6C)alkyl optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L is attached meta or para on ring A with respect to the point of attachment of the ethynyl group and represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)- NR^9 wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^6 is selected from halo, cyano, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -N(R^c)CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3; and when m is at least 2 then two substituents on adjacent carbon atoms in ring B may together represent a methylenedioxy group;
and pharmaceutically acceptable salts thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, (1-6C)alkylamino includes methylamino and ethylamino, and di-[(1-6Calkyl]amino includes dimethylamino and diethylamino.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

Suitable 5 or 6 membered heteroaryl rings include, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, 1,3,5-triazenyl or pyrazinyl. Particular 5 or 6 membered heteroaryl rings include imidazolyl, pyridyl, thiazolyl, thiadiazolyl, pyrimidinyl, isoxazolyl, isothiazolyl and pyrazolyl.

Suitable saturated or partially saturated 3 to 7 membered heterocyclic rings include, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 2,3-dihydro-1,3-thiazolyl, 1,3-thiazolidinyl, 1,3-oxazolidinyl, oxepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, thiamorpholinyl (perhydro-1,4-thiazinyl), (8-oxa-3-azabicyclo[3.2.1]octyl), (7-oxa-3-azabicyclo[3.1.1]heptyl), perhydroazepinyl, perhydrooxazepinyl, tetrahydro-1,4-thiazinyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl, more preferably tetrahydrofuran-3-yl, tetrahydropyran-4-yl, pyrrolidin-3-yl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-4-yl or piperazin-1-yl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl. The saturated or partially saturated 3 to 7 membered heterocyclic rings are optionally substituted by one or more (1-6C) alkyl groups and/or by one or more hydroxy.

Suitable 8, 9 or 10 membered bicyclic groups include thieno[2,3-b]furanyl, imidazolo[2,1-b]thiazolyl, dihydrocyclopentathiazolyl, tetrahydrocyclopenta[c]pyrazolyl, furo[3,2-b]furanyl, pyrrolopyrrole, thienopyrazolyl, thieno[2,3-b]thiophenyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolin-yl, benzo[b]furanyl, benzo[b]thiophenyl, IH-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, chromanyl, isochromanyl, indenyl, naphthalenyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxol-5-yl, decalin and norbornane. Particular 8, 9 or 10 membered bicyclic groups include thieno[2,3-b]furanyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolin-yl, benzo[b]furanyl, benzo[b]thiophenyl, IH-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl,

quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, chromanyl, isochromanyl, indenyl, naphthalenyl, 2,3-dihydro-1,4-benzodioxinyl and 1,3-benzodioxol-5-yl.

The bicyclic groups are optionally substituted by one or more groups R^6 as hereinbefore defined.

The group A may particularly be attached to the ethynyl group via a carbon atom in the aryl group or in the 5 or 6 membered heteroaryl ring. The group B may particularly be attached to the group L via a carbon atom.

Suitable values for any of the substituents herein, for example the 'R' groups (R^1 to R^6) or for various groups within a A, B or L group include:

for halo	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (1-6C)alkylsulfonyl:	methylsulfonyl and ethylsulfonyl;
for mono(1-6C)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for (2-6C)alkanoyl:	acetyl and propionyl;
for (1-6C)alkanoylamino:	acetamido and propionamido;
for amino-(1-6C)alkyl:	aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
for (1-6C)alkylamino-(1-6C)alkyl:	methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-ethylaminopropyl;
for di-[(1-6C)alkyl]amino-(1-6C)alkyl:	dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
for halogeno-(1-6C)alkyl:	chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;
for hydroxy-(1-6C)alkyl:	hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;

for (1-6C)alkoxy-(1-6C)alkyl:	methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
for cyano-(1-6C)alkyl:	cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;
for (3-7C)cycloalkyl:	cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl;
for (1-6C)alkoxy(1-6C)alkoxy:	methoxymethoxy, methoxyethoxy, methoxypropoxy, methoxybutoxy, methoxyhexoxy, ethoxyethoxy, ethoxypropoxy, ethoxybutoxy, propoxypropoxy and propoxybutoxy;
for (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy:	methoxymethoxymethoxy, methoxyethoxyethoxy, methoxypropoxymethoxy, methoxybutoxyethoxy, methoxyhexoxymethoxy, ethoxyethoxyethoxy, ethoxypropoxyethoxy, ethoxybutoxymethoxy, propoxypropoxymethoxy and propoxybutoxymethoxy;
for mono(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl; and
for di-[(1-6C)alkyl]carbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl.

When in this specification reference is made to a (1-4C)alkyl group it is to be understood that such groups refer to alkyl groups containing up to 4 carbon atoms. A skilled person will realise that representative examples of such groups are those listed above under (1-4C)alkyl that contain up to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl and tert-butyl. Similarly, reference to a (1-3C)alkyl group refers to alkyl groups containing up to 3 carbon atoms such as methyl, ethyl, propyl and isopropyl. A similar convention is adopted for the other groups listed above such as (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl and (2-4C)alkanoyl.

It is to be understood that certain compounds of the formula I may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which exhibit an inhibitory effect on a Tie2 receptor tyrosine kinase.

It is also to be understood that certain compounds of the formula I may exhibit polymorphism, and that the invention encompasses all such forms which exhibit an inhibitory effect on a Tie2 receptor tyrosine kinase.

It is also to be understood that the invention relates to all tautomeric forms of the compounds of the formula I forms which exhibit an inhibitory effect on a Tie2 receptor tyrosine kinase.

A suitable pharmaceutically acceptable salt of a compound of the formula I is, for example, an acid-addition salt of a compound of the formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulfuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, compounds of the formula I, or pharmaceutically acceptable salts thereof, wherein, unless otherwise stated, each of R^1, R^2, R^3, R^4, R^5, R^6, A, B, L, m and n has any of the meanings defined hereinbefore or in paragraphs (a) to (eeee) hereinafter:-

(a) L is $CH_2CON(R^9)$, wherein R^9 is H or (1-6C)alkyl (particularly R^9 is H);

(b) L is $N(R^8)COCH_2$, wherein R^8 is H or (1-6C)alkyl (particularly R^8 is H);

(c) L is $N(R^8)CON(R^9)$, wherein R^8 and R^9 are independently selected from H and (1-6C)alkyl (particularly R^8 and R^9 are both H);

(d) L is $N(R^8)C(O)$-O-, wherein R^8 is H or (1-6C)alkyl (particularly R^8 is H);

(e) L is –O-(CO)- NR^9, wherein R^9 is H or (1-6C)alkyl (particularly R^9 is H);

(f) Ring B-R^6, where m is 1 or 2, is selected from 2-methoxyphenyl, 2-fluoro-5-(trifluoromethyl)phenyl, 5-tert-butylisoxazol-3-yl, 3-(trifluoromethyl)phenyl, 3-morpholin-4-ylphenyl, 3-methylisoxazol-5-yl, 5-tert-butyl-1,3,4-thiadiazol-2-yl and 3-acetylaminophenyl;

(g) R^1 and R^2 are both hydrogen, R^3 and R^4 are both hydrogen, n is 0, L is –NHC(O)NH-, and ring B-R^6, where m is 1 or 2, is selected from 2-methoxyphenyl, 2-fluoro-5-(trifluoromethyl)phenyl, 5-tert-butylisoxazol-3-yl, 3-(trifluoromethyl)phenyl, 3-morpholin-4-ylphenyl, 3-methylisoxazol-5-yl, 5-tert-butyl-1,3,4-thiadiazol-2-yl and 3-acetylaminophenyl;

(h) R^1 and R^2 are independently selected from hydrogen, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group –N(R^d)CO(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more (for example 1 or 2) hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and (1-6C)alkoxy groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or -C(O)$(CH_2)_z$Y wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

(i) R^1 and R^2 are independently selected from hydrogen, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl or (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

(j) R^1 and R^2 are independently selected from hydrogen, (1-6C)alkanoyl and (1-6C)alkyl;

wherein the (1-6C)alkyl and the (1-6C)alkanoyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

(k) R^1 is hydrogen and R^2 is selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

wherein the phenyl is optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

(l) R^1 is hydrogen and R^2 is selected from hydrogen, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl or (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

(m) R^1 is hydrogen and R^2 is selected from hydrogen, (1-6C)alkanoyl and (1-6C)alkyl;

wherein the (1-6C)alkyl and the (1-6C)alkanoyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (h);

(n) R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from hydroxy, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group $-N(R^d)CO$(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more (for example 1 or 2) hydroxy groups;

and wherein the phenyl is optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and (1-6C)alkoxy groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, or a saturated or partially saturated 3 to 7 membered heterocyclic ring or $-C(O)(CH_2)_zY$ wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by hydroxy;

(o) R^1 and R^2 are independently selected from hydrogen, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl or (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

(p) R^1 and R^2 are independently selected from hydrogen, (1-6C)alkanoyl and (1-6C)alkyl;

wherein the (1-6C)alkyl and the (1-6C)alkanoyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

(q) R^1 is hydrogen and R^2 is selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

and wherein the phenyl is optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

(r) R^1 is hydrogen and R^2 is selected from hydrogen, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl or (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

(s) R^1 is hydrogen and R^2 is selected from hydrogen, (1-6C)alkanoyl and (1-6C)alkyl;

wherein the (1-6C)alkyl and the (1-6C)alkanoyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (n);

(t) R^1 is hydrogen and R^2 is selected from hydrogen, (1-6C)alkanoyl and (1-6C)alkyl;

wherein the (1-6C)alkyl and the (1-6C)alkanoyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from hydroxy, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkoxy, amino, mono(1-3C)alkylamino, di(1-3C)alkylamino, carbamoyl or an alkanoylamino group $-N(R^d)CO(1\text{-}3C)alkyl$ in which R^d is hydrogen or (1-3C)alkyl, or a saturated 5 or 6 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein the (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkoxy groups and the (1-3C)alkyl groups of the mono(1-3C)alkylamino, di-[(1-3C)alkyl]amino and/or alkanoylamino groups are optionally substituted by one or more (for example 1 or 2) hydroxy groups;

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-3C)alkylamino or di-[(1-3C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or $-C(O)(CH_2)_zY$ wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by hydroxy;

(u) R^1 is hydrogen and R^2 is selected from hydrogen, (1-3C)alkanoyl and (1-3C)alkyl;

wherein the (1-3C)alkyl and the (1-3C)alkanoyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (t);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (t);

(v) R^1 is hydrogen and R^2 is selected from hydrogen and (1-6C)alkyl (particularly (1-3C)alkyl);

wherein the (1-6C)alkyl (particularly (1-3C)alkyl) group is optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (t);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (t);

(w) R^1 is hydrogen and R^2 is (1-6C)alkyl (particularly (1-3C)alkyl);

wherein the (1-6C)alkyl (particularly (1-3C)alkyl) group is optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (t);

and wherein any heterocyclic and heteroaryl rings within R^2 are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, as hereinbefore defined in (t);

(x) R^1 and R^2 are independently selected from hydrogen, methyl, ethyl, propyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(2-hydroxyethoxy)ethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 2-(isopropylamino)ethyl, 3-(isopropylamino)propyl, 2-(dimethylamino)ethyl, 3-(dimethylamino)propyl, 4-(dimethylamino)butyl, 2-(dimethylamino)-1-methylethyl, carbamoylmethyl, 2-carbamoylethyl, 3-carbamoylpropyl, 2-(2-methoxyethoxy)acetyl, N-ethyl-2-hydroxyacetamide, 2-morpholin-4-ylethyl, 3-morpholin-4-ylpropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 3-(4-methylpiperazin-1-yl)propyl, 3-piperidin-1-ylpropyl, 2-piperidin-1-ylethyl, 2-(1H-imidazol-4-yl)ethyl, 2-pyridin-2-ylethyl, 3-(1H-imidazol-1-yl)propyl and 2-pyridin-4-ylethyl;

(y) R^1 is hydrogen and R^2 is selected from hydrogen, methyl, ethyl, propyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-(2-hydroxyethoxy)ethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 2-(isopropylamino)ethyl, 3-(isopropylamino)propyl, 2-(dimethylamino)ethyl, 3-(dimethylamino)propyl, 4-(dimethylamino)butyl, 2-(dimethylamino)-1-methylethyl, carbamoylmethyl, 2-carbamoylethyl, 3-carbamoylpropyl, 2-(2-methoxyethoxy)acetyl, N-ethyl-2-hydroxyacetamide, 2-morpholin-4-ylethyl, 3-morpholin-4-ylpropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 3-(4-methylpiperazin-1-yl)propyl, 3-piperidin-1-ylpropyl, 2-piperidin-1-ylethyl, 2-(1H-imidazol-4-yl)ethyl, 2-pyridin-2-ylethyl, 3-(1H-imidazol-1-yl)propyl and 2-pyridin-4-ylethyl;

(z) R^1 is hydrogen and R^2 is selected from 2-morpholin-4-ylethyl, 3-morpholin-4-ylpropyl, 3-piperidin-1-ylpropyl, 2-piperidin-1-ylethyl, 2-pyrrolidin-1-ylethyl and 3-pyrrolidin-1-ylpropyl;

(aa) R^1 and R^2 are both hydrogen;

(bb) R^1 and R^2 are both (1-6C)alkyl (particularly (1-3C)alkyl);

(cc) R^1 and R^2 are both methyl;

(dd) R^3 and R^4 are independently selected from hydrogen and (1-6C)alkyl;

wherein the (1-6C)alkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said

heterocyclic and heteroaryl rings are optionally independently substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

(ee) R^3 and R^4 are independently selected from hydrogen and (1-6C)alkyl;

wherein the (1-6C)alkyl groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl;

(ff) R^3 and R^4 are both hydrogen;

(gg) A is selected from phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and 1,3,5-triazenyl;

(hh) A is selected from phenyl, pyrrolyl, thienyl, oxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and 1,3,5-triazenyl;

(ii) A is selected from phenyl, thiazolyl, thiadiazolyl, pyridyl and pyrimidinyl;

(jj) A is phenyl;

(kk) A is phenyl and n is 0;

(ll) n is 0, 1 or 2 (particularly 0 or 1, more particularly 0);

(mm) n is 1 or 2 and R^5 is independently selected from cyclopropyl, halo, (1-6C)alkoxy and (1-6C)alkyl, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by cyano or one or more (for example 1 or 2) fluoro;

(nn) L is $N(R^8)COC(R^aR^b)$, wherein R^8 independently represents H or (1-6C)alkyl, R^a is hydrogen and R^b independently represents H or (1-6C)alkyl (particularly R^b is (1-3C)alkyl, such as methyl);

(oo) L is attached meta on ring A with respect to the point of attachment of the ethynyl group;

(pp) L is attached meta on ring A with respect to the point of attachment of the ethynyl group and represents $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$ or $N(R^8)C(O)$-O-, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or

(1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

(qq) L is attached meta on ring A with respect to the point of attachment of the ethynyl group and represents $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$ or $N(R^8)C(O)$-O-, wherein R^8 and R^9 independently represent H or (1-3C)alkyl and wherein R^a and R^b independently represent H or (1-3C)alkyl;

(rr) L is attached para on ring A with respect to the point of attachment of the ethynyl group and represents $N(R^8)COC(R^aR^b)$ or $N(R^8)CON(R^9)$, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

(ss) L is attached para on ring A with respect to the point of attachment of the ethynyl group and represents $N(R^8)COC(R^aR^b)$ or $N(R^8)CON(R^9)$, wherein R^8 and R^9 independently represent H or (1-3C)alkyl and wherein R^a and R^b independently represent H or (1-3C)alkyl;

(tt) A is selected from phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and 1,3,5-triazenyl (particularly phenyl, thiazolyl, thiadiazolyl, pyridyl and pyrimidinyl);

n is 0; and

L is attached meta on ring A with respect to the point of attachment of the ethynyl group and represents $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$ or $N(R^8)C(O)$-O-, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

(uu) A is selected from phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and 1,3,5-triazenyl (particularly phenyl, thiazolyl, thiadiazolyl, pyridyl and pyrimidinyl);

n is 0; and

L is attached meta on ring A with respect to the point of attachment of the ethynyl group and represents $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$ or $N(R^8)C(O)$-O-, wherein R^8 and R^9 independently represent H or (1-3C)alkyl and wherein R^a and R^b independently represent H or (1-3C)alkyl;

(vv) B is selected from a (4-6C)cycloalkyl ring, a saturated or partially saturated 4 to 6 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

(ww) B is selected from a (4-6C)cycloalkyl ring, a saturated or partially saturated 4 to 6 membered heterocyclic ring, an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

(xx) B is selected from cyclopentyl, cyclohexyl, piperidinyl, tetrahydropyranyl, phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, 2,3-dihydro-1,4-benzodioxinyl and 1,3-benzodioxol-5-yl;

(yy) B is selected from phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, 2,3-dihydro-1,4-benzodioxinyl and 1,3-benzodioxol-5-yl;

(zz) B is selected from phenyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyridyl and pyrazolyl;

(aaa) B is selected from phenyl, isoxazolyl, thiadiazolyl and pyrazolyl;

(bbb) B is phenyl;

(ccc) B is isoxazolyl;

(ddd) B is pyrazolyl;

(eee) B is thiadiazolyl;

(fff) B is a (3-7C)cycloalkyl ring (particularly a (4-6C)cycloalkyl ring);

(ggg) B is a saturated or partially saturated 3 to 7 (particularly 4 to 6) membered heterocyclic ring that contains one or two heteroatoms (particularly one heteroatom) selected from oxygen and nitrogen;

(hhh) B is a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2 or 3 (particularly 1 or 2) heteroatoms independently selected from N and O and which is saturated, partially saturated or aromatic;

(iii) A is phenyl;

n is 0; and

B is selected from a (4-6C)cycloalkyl ring, a saturated or partially saturated 4 to 6 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

(jjj) A is phenyl;

n is 0; and

B is selected from phenyl, isoxazolyl, thiadiazolyl and pyrazolyl;

(kkk) A is selected from phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and 1,3,5-triazenyl;

n is 0;

L is attached meta on ring A with respect to the point of attachment of the ethynyl group and represents $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$ or $N(R^8)C(O)$-O-, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl; and

B is selected from phenyl, isoxazolyl, thiadiazolyl and pyrazolyl;

(lll) A is selected from phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and 1,3,5-triazenyl;

n is 0;

L is attached meta on ring A with respect to the point of attachment of the ethynyl group and represents $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$ or $N(R^8)C(O)$-O-, wherein R^8 and R^9 independently represent H or (1-3C)alkyl and wherein R^a and R^b independently represent H or (1-3C)alkyl; and

B is selected from phenyl, isoxazolyl, thiadiazolyl and pyrazolyl;

(mmm) m is 0, 1 or 2 (particularly 1 or 2);

(nnn) m is 1;

(ooo) m is 2;

(ppp) R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring or an alkanoylamino group -N(R^c)CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

(qqq) R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring or an alkanoylamino group -N(R^c)CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from cyano, fluoro, hydroxy and amino (particularly fluoro);

(rrr) R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring or an alkanoylamino group -N(R^c)CO(1-6C)alkyl in which R^c is H or (1-3C)alkyl; or R^6 is selected from (1-4C)alkyl or (1-4C)alkoxy, wherein the (1-4C)alkyl and the (1-4C)alkoxy groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from cyano, fluoro, hydroxy and amino (particularly fluoro);

(sss) R^6 is selected from fluoro, chloro, cyano, acetylamino, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, trifluoromethyl, cyclopropyl, methoxy, ethoxy, propoxy and butoxy;

(ttt) B is selected from cyclopentyl, cyclohexyl, piperidinyl, tetrahydropyranyl, phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, 2,3-dihydro-1,4-benzodioxinyl and 1,3-benzodioxol-5-yl;

m is 1 or 2; and

R^6 is independently selected from halo, cyano, a (3-7C)cycloalkyl ring or an alkanoylamino group -N(R^c)CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are

optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from cyano, fluoro, hydroxy and amino (particularly fluoro);

(uuu) B is selected from cyclopentyl, cyclohexyl, piperidinyl, tetrahydropyranyl, phenyl, furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, 2,3-dihydro-1,4-benzodioxinyl and 1,3-benzodioxol-5-yl;

m is 1 or 2; and

R^6 is independently selected from fluoro, chloro, cyano, acetylamino, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, trifluoromethyl, cyclopropyl, methoxy, ethoxy, propoxy and butoxy;

(vvv) B is selected from phenyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyrazolyl and pyridyl;

m is 1 or 2; and

R^6 is independently selected from halo, cyano, a (3-7C)cycloalkyl ring or an alkanoylamino group -N(R^c)CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups (for example 1 or 2), which may be the same or different, selected from cyano, fluoro, hydroxy and amino (particularly fluoro);

(www) B is selected from phenyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyrazolyl and pyridyl;

m is 1 or 2; and

R^6 is independently selected from fluoro, chloro, cyano, acetylamino, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, trifluoromethyl, cyclopropyl, methoxy, ethoxy, propoxy and butoxy;

(xxx) B is phenyl;

m is 1 or 2; and

R^6 is independently selected from fluoro, chloro, cyano, acetylamino, trifluoromethyl, cyclopropyl, methoxy, ethoxy, propoxy and butoxy;

(yyy) B is phenyl;

m is 1 or 2; and

R^6 is independently selected from fluoro and trifluoromethyl;

(zzz) B is isoxazolyl;

m is 1 or 2; and

R^6 is independently selected from fluoro, chloro, cyano, acetylamino, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, trifluoromethyl, cyclopropyl, methoxy, ethoxy, propoxy and butoxy;

(aaaa) B is isoxazolyl;

m is 1 or 2; and

R^6 is independently selected from methyl, ethyl, propyl, isopropyl, butyl, tert-butyl (particularly methyl and tert-butyl, more particularly tert-butyl);

(bbbb) B is pyrazolyl;

m is 1 or 2; and

R^6 is independently selected from fluoro, chloro, cyano, acetylamino, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, trifluoromethyl, cyclopropyl, methoxy, ethoxy, propoxy and butoxy;

(cccc) B is thiadiazolyl;

m is 1 or 2; and

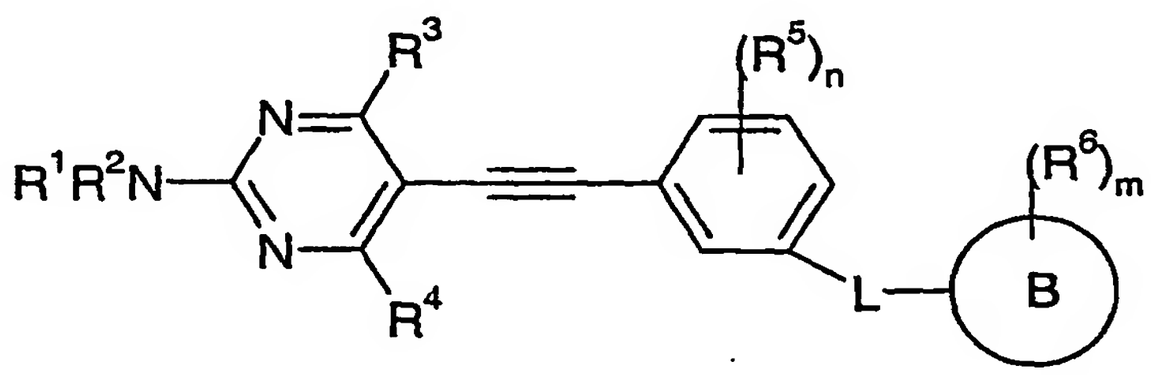
R^6 is independently selected from fluoro, chloro, cyano, acetylamino, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, trifluoromethyl, cyclopropyl, methoxy, ethoxy, propoxy and butoxy;

(dddd) Ring B-R^6 wherein m is 0, 1 or 2 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 2-fluoro-5-(trifluoromethyl)phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-acetamidophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 5-tert-butyl-1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, 5-ethyl-1,3,4-thiadiazol-2-yl, 5-isopropyl-1,3,4-thiadiazol-2-yl, 5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl, 4-tert-butyl-1,3-thiazol-2-yl, 5-cyclopropyl-1,3,4-thiadiazol-2-yl, 1-methyl-3-cyclopropyl-pyrazol-5-yl, 1-tert-butyl-3-cyclopropyl-pyrazol-5-yl, 3-methylisothiazol-5-yl, 3-methylisoxazol-5-yl, 5-methylisoxazol-3-yl, 5-tert-butylisoxazol-3-yl, 4-(trifluoromethyl)pyridin-2-yl, 2-oxopiperidin-3-yl, 2,2-dimethyltetrahydro-2H-pyran-4-yl, 2,3-dihydro-1,4-benzodioxinyl and 1,3-benzodioxol-5-yl; and

(eeee) Ring B-R^6 wherein m is 1 or 2 is selected from 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-

(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 2-fluoro-5-(trifluoromethyl)phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-acetamidophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 5-tert-butyl-1,3,4-thiadiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl, 5-ethyl-1,3,4-thiadiazol-2-yl, 5-isopropyl-1,3,4-thiadiazol-2-yl, 5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl, 4-tert-butyl-thiazol-2-yl, 5-cyclopropyl-1,3,4-thiadiazol-2-yl, 1-methyl-3-cyclopropyl-pyrazol-5-yl, 1-tert-butyl-3-cyclopropyl-pyrazol-5-yl, 3-methylisothiazol-5-yl, 3-methylisoxazol-5-yl, 5-methylisoxazol-3-yl, 5-tert-butylisoxazol-3-yl, 4-(trifluoromethyl)pyridin-2-yl, 2-oxopiperidin-3-yl and 2,2-dimethyltetrahydro-2H-pyran-4-yl.

A particular embodiment of the compounds of the Formula I is a compound of the Formula Ia:



Formula Ia

wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group $–N(R^d)CO$(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-

6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups independently selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring, or $-C(O)(CH_2)_zY$ wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy,

wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of R^3 and R^4 is as defined above and the other represents a group $-NR^1R^2$ as defined above;

R^5 is selected from cyclopropyl, cyano, halo, (1-6C)alkoxy or (1-6C)alkyl, wherein the (1-6C)alkyl and (1-6C)alkoxy groups are optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)-NR^9, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

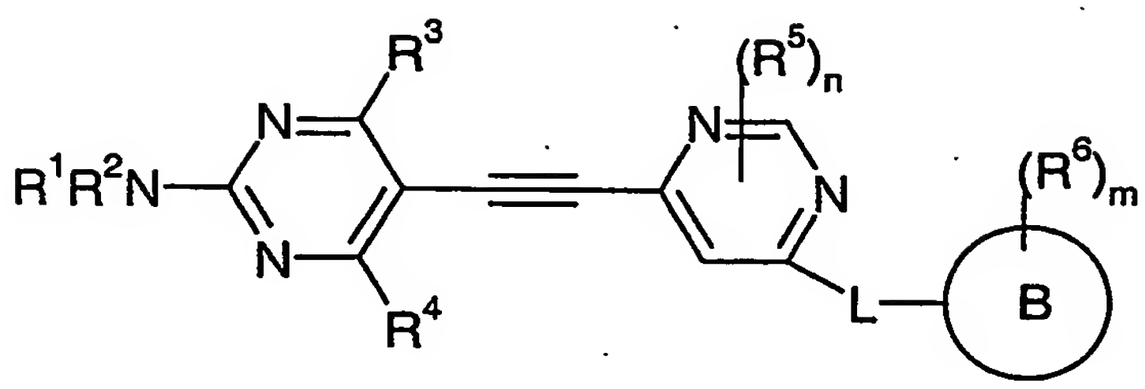
$\mathbf{R^6}$ is selected from halo, cyano, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -$N(R^c)$CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or

$\mathbf{R^6}$ is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3;

and when B is a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a saturated or partially saturated 8, 9 or 10 membered bicyclic group, the rings and the bicyclic group optionally bears 1 or 2 oxo or thioxo substituents;
and pharmaceutically acceptable salts thereof.

Another particular embodiment of the compounds of the Formula I is a compound of the Formula Ib:



Formula Ib

wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group –$N(R^d)$CO(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups independently selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring, or -C(O)$(CH_2)_z$Y wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-

6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy,

wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of **R^3** and **R^4** is as defined above and the other represents a group **$-NR^1R^2$** as defined above;

R^5 is selected from cyclopropyl, cyano, halo, (1-6C)alkoxy or (1-6C)alkyl, wherein the (1-6C)alkyl and (1-6C)alkoxy groups are optionally substituted by cyano or by one or more fluoro;

n is 0, 1 or 2;

L represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)-NR^9, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4

heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

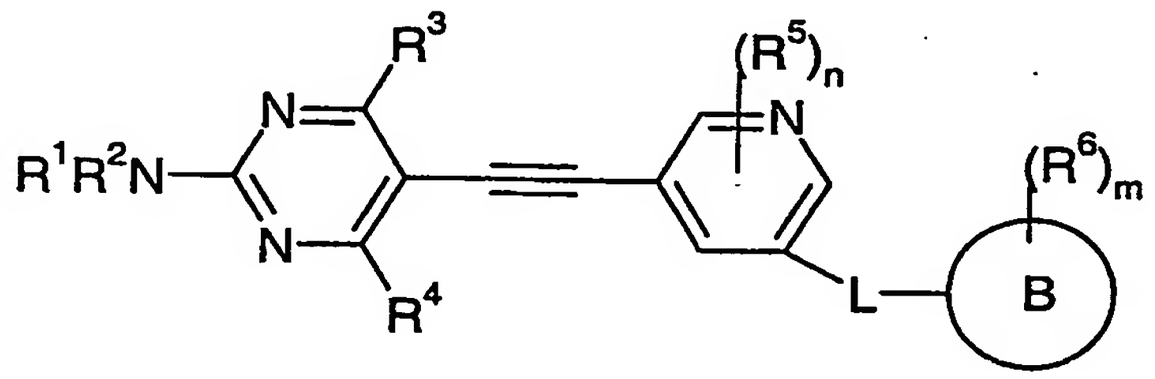
R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -N(R^c)CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3;

and when B is a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a saturated or partially saturated 8, 9 or 10 membered bicyclic group, the rings and the bicyclic group optionally bears 1 or 2 oxo or thioxo substituents;
and pharmaceutically acceptable salts thereof.

Another particular embodiment of the compounds of the Formula I is a compound of the Formula Ic:



Formula Ic

wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl(CH_2)$_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl(CH_2)$_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group $-N(R^d)CO(1-6C)$alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups independently selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring, or $-C(O)(CH_2)_zY$ wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy,

wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following:

(1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of R^3 and R^4 is as defined above and the other represents a group $-NR^1R^2$ as defined above;

R^5 is selected from cyclopropyl, cyano, halo, (1-6C)alkoxy or (1-6C)alkyl, wherein the (1-6C)alkyl and (1-6C)alkoxy groups are optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)-NR^9, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -$N(R^c)$CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or

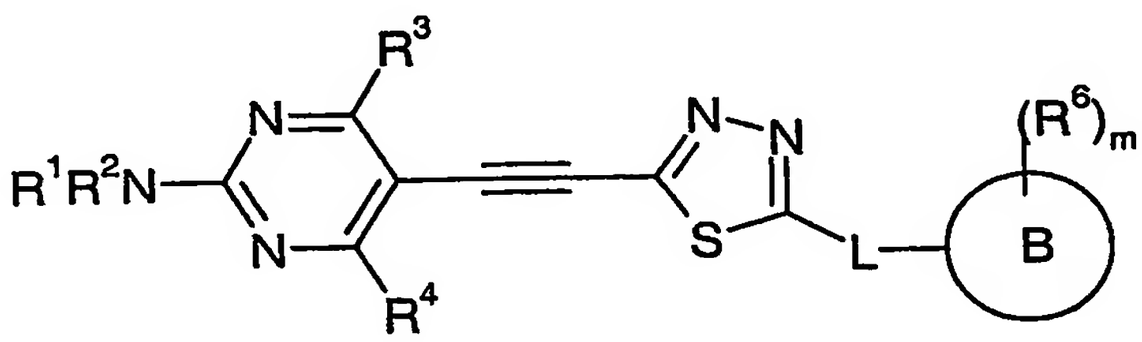
R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3;

and when B is a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a saturated or partially saturated 8, 9 or 10 membered bicyclic group, the rings and the bicyclic group optionally bears 1 or 2 oxo or thioxo substituents;

and pharmaceutically acceptable salts thereof.

Another particular embodiment of the compounds of the Formula I is a compound of the Formula Id:



Formula Id

wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group $–N(R^d)CO$(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups independently selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-

6C)alkyl]amino, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring, or $-C(O)(CH_2)_zY$ wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy,

wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of R^3 and R^4 is as defined above and the other represents a group $-NR^1R^2$ as defined above;

L represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)-NR^9, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl,

oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -N(R^c)CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3;

and when B is a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring or a saturated or partially saturated 8, 9 or 10 membered bicyclic group, the rings and the bicyclic group optionally bears 1 or 2 oxo or thioxo substituents;

and pharmaceutically acceptable salts thereof.

Specific compounds of the present invention are one or more of the following:

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-*N'*-[2-fluoro-5-(trifluoromethyl)phenyl]urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[2-(trifluoromethyl)phenyl]urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[4-(trifluoromethyl)phenyl]urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2-fluorophenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-fluorophenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(4-fluorophenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-methoxyphenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2,5-difluorophenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-1,3-benzodioxol-5-ylurea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2-methoxyphenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(4-methoxyphenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3,4-difluorophenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-cyanophenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-chlorophenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-cyclopentylurea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3,5-difluorophenyl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-tert-butyl-1,3,4-thiadiazol-2-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-methylisoxazol-5-yl)urea

N-(3-{[({3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}amino)carbonyl]amino}phenyl) cetamide

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-tert-butylisoxazol-3-yl)urea

Phenyl {3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}carbamate

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2-oxopiperidin-3-yl)urea

N-(5-tert-butylisoxazol-3-yl)-N'-(3-{[2-(methylamino)pyrimidin-5-yl]ethynyl}phenyl)urea

N-(5-tert-butylisoxazol-3-yl)-N'-(3-{[2-(dimethylamino)pyrimidin-5-yl]ethynyl}phenyl)urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-methoxyethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[3-(1H-imidazol-1-yl)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(3-methoxypropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-hydroxyethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-[3-({2-[(2-aminoethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]-N'-(5-tert-butylisoxazol-3-yl)urea

N-[3-({2-[(3-aminopropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]-N'-(5-tert-butylisoxazol-3-yl)urea

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[2-(dimethylamino)ethyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N-2-(5-{[3-({[(5-tert-butylisoxazol-3-yl)amino]carbonyl}amino)phenyl]ethynyl}pyrimidin-2-yl)glycinamide

N-3-(5-{[3-({[(5-tert-butylisoxazol-3-yl)amino]carbonyl}amino)phenyl]ethynyl}pyrimidin-2-yl)-beta-alaninamide

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[2-(1H-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-pyridin-2-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[3-(isopropylamino)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-pyridin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-methylisoxazol-3-yl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(3-methylisothiazol-5-yl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(3-fluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(4-methoxyphenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(2-fluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(2,5-difluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(3,4-difluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-[2-fluoro-5-(trifluoromethyl)phenyl]-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]-N'-[4-(trifluoromethyl)phenyl]urea

N-1,3-benzodioxol-5-yl-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(4-fluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(3-chlorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-methylisoxazol-3-yl)-N'-[3-({2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[3-({2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-[2-fluoro-5-(trifluoromethyl)phenyl]-N'-[3-({2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-methylisoxazol-3-yl)-N'-[3-({2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[3-({2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-[2-fluoro-5-(trifluoromethyl)phenyl]-N'-[3-({2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-methylisoxazol-3-yl)-N'-[4-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-[4-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[4-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-[2-fluoro-5-(trifluoromethyl)phenyl]-N'-[4-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-{[3-({[(5-tert-butylisoxazol-3-yl)amino]carbonyl}amino)phenyl]ethynyl}pyrimidin-2-yl)-2-(2-methoxyethoxy)acetamide

N-{6-[(2-aminopyrimidin-5-yl)ethynyl]pyridin-2-yl}-N'-(5-tert-butylisoxazol-3-yl)urea

N-{2-[(2-aminopyrimidin-5-yl)ethynyl]pyridin-4-yl}-N'-(5-tert-butylisoxazol-3-yl)urea

N-{5-[(2-aminopyrimidin-5-yl)ethynyl]-1,3-thiazol-2-yl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

N-{5-[(2-aminopyrimidin-5-yl)ethynyl]-1,3,4-thiadiazol-2-yl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

N-{5-[(2-aminopyrimidin-5-yl)ethynyl]-1,3-thiazol-2-yl}-*N'*-(5-*tert*-butylisoxazol-3-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(2-methoxyphenyl)acetamide

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-phenylacetamide

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(3-methoxyphenyl)acetamide

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-[3-(trifluoromethyl)phenyl]acetamide

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-[4-(trifluoromethyl)phenyl]acetamide

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(3-methylisoxazol-5-yl)acetamide

N-{4-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(2-methoxyphenyl)acetamide

N-{4-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(3-methylisoxazol-5-yl)acetamide

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2,2-dimethyltetrahydro-2H-pyran-4-yl)urea

N-{6-[(2-aminopyrimidin-5-yl)ethynyl]pyrimidin-4-yl}-N'-(5-tert-butylisoxazol-3-yl)urea

N'-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N-(5-tert-butylisoxazol-3-yl)-N-methylurea

and pharmaceutically acceptable salts thereof.

Further specific compounds of the present invention are one or more of the following:

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(1-tert-butyl-3-cyclopropyl-1H-pyrazol-5-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-methylisoxazol-3-yl)urea

N-{5-[(2-aminopyrimidin-5-yl)ethynyl]pyridin-3-yl}-N'-(5-tert-butylisoxazol-3-yl)urea

N-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(3-methylisoxazol-5-yl)-N'-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(2-methoxyphenyl)-N'-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(3-fluorophenyl)-N'-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N'-{4-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N-(5-tert-butylisoxazol-3-yl)-N-methylurea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-phenylurea

N-[3-({2-[(4-aminobutyl)amino]pyrimidin-5-yl}ethynyl)phenyl]-N'-(5-tert-butylisoxazol-3-yl)urea

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-piperidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[2-(isopropylamino)ethyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[2-(2-hydroxyethoxy)ethyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea

N-{2-[(5-{[3-({[(5-tert-butylisoxazol-3-yl)amino]carbonyl}amino)phenyl]ethynyl}pyrimidin-2-yl)amino]ethyl}-2-hydroxyacetamide

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[4-(dimethylamino)butyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

N'-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N-methyl-N-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]urea

N-phenyl-N'-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-(5-methylisoxazol-3-yl)-N'-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-tert-butylisoxazol-3-yl)-N-methylurea

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[2-(dimethylamino)-1-methylethyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

phenyl {3-[(2-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}carbamate

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(4-tert-butyl-1,3-thiazol-2-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-methyl-1,3,4-thiadiazol-2-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-ethyl-1,3,4-thiadiazol-2-yl)urea

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-isopropyl-1,3,4-thiadiazol-2-yl)urea

N-{3-[(2-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}-N'-(5-methylisoxazol-3-yl)urea

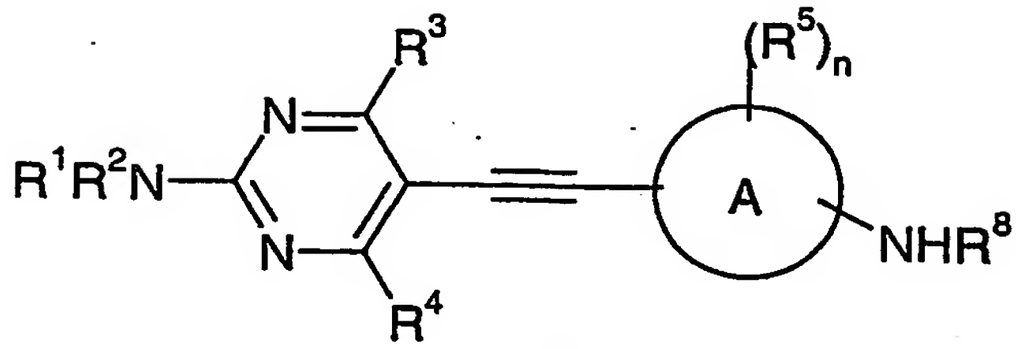
N-{3-[(2-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}-N'-phenylurea

and pharmaceutically acceptable salts thereof.

A compound of the Formula I, or a pharmaceutically acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

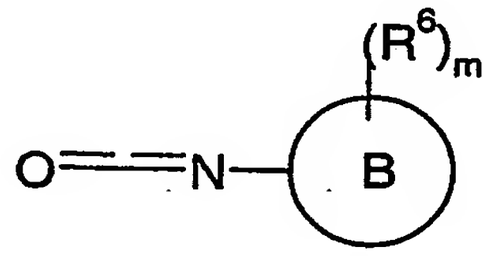
According to a further aspect of the present invention provides a process for preparing a compound of formula I or a pharmaceutically acceptable salt thereof (wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^a, R^b, L, ring A and ring B, n and m are, unless otherwise specified, as defined in formula I) as described schematically below.

Process (a) For compounds of the formula I wherein L is $N(R^8)CON(H)$, the reaction of a compound of the formula II:



II

wherein R^1, R^2, R^3, R^4, R^5, R^8, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an isocyanate of the formula IV:

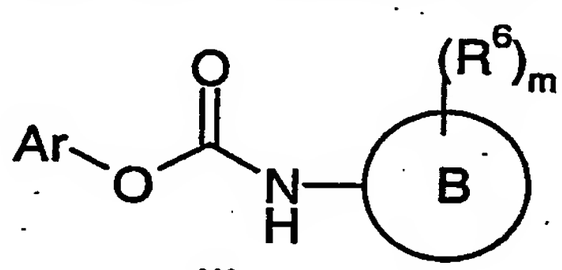


IV

wherein R^6, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (b) For compounds of the formula I wherein L is $N(R^8)CON(H)$, the reaction of a compound of the formula II as defined above with an aryl carbamate of the formula III:

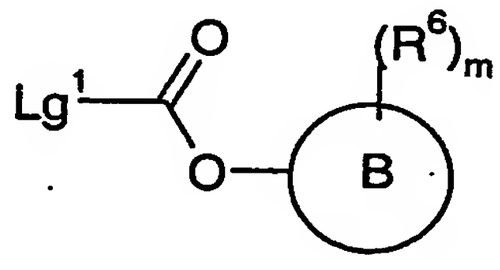


III

wherein Ar is a suitable aryl group, for example phenyl, and R^6, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (c) For compounds of the formula I wherein L is $N(R^8)C(O)$-O-, the reaction of a compound of the formula II as defined above with a compound of the formula XI:

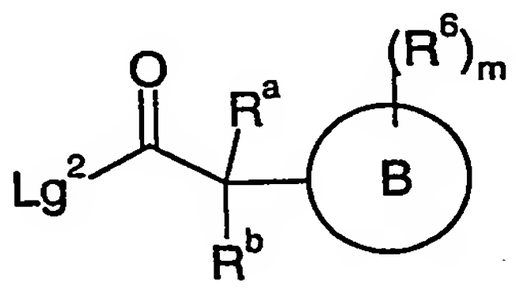


XI

wherein Lg^1 is a suitable displaceable group for example halogeno (such as fluoro, chloro or bromo) and R^6, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (d) For compounds of the formula I wherein L is $N(R^8)C(O)C(R^aR^b)$, the reaction of a compound of the formula II as defined above with a compound of the formula IX:

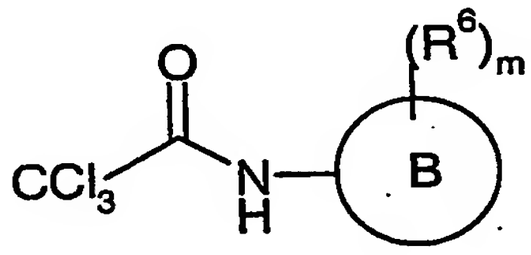


IX

wherein Lg^2 is a suitable displaceable group for example hydroxy, halogeno (such as fluoro, chloro or bromo), R^x-C(O)-O- or R^x-O- (wherein R^x is a suitable alkyl or aryl group) and R^6, R^a, R^b, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (e) For compounds of the formula I wherein L is $N(R^8)CON(H)$, the reaction of a compound of the formula II as defined above with a trichloroacetylamine of the formula XIII:

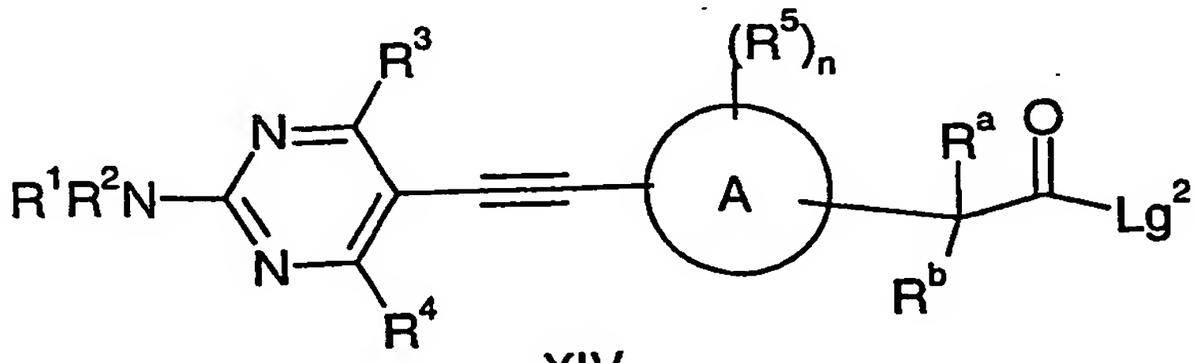


XIII

wherein R^6, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

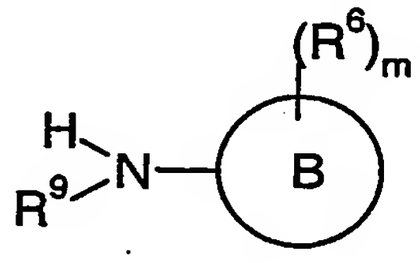
or

Process (f) For compounds of the formula I wherein L is $C(R^aR^b)CON(R^9)$, the reaction of a compound of the formula XIV:



XIV

wherein Lg^2 is a suitable displaceable group as described above and R^1, R^2, R^3, R^4, R^5, R^a, R^b, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula XV:

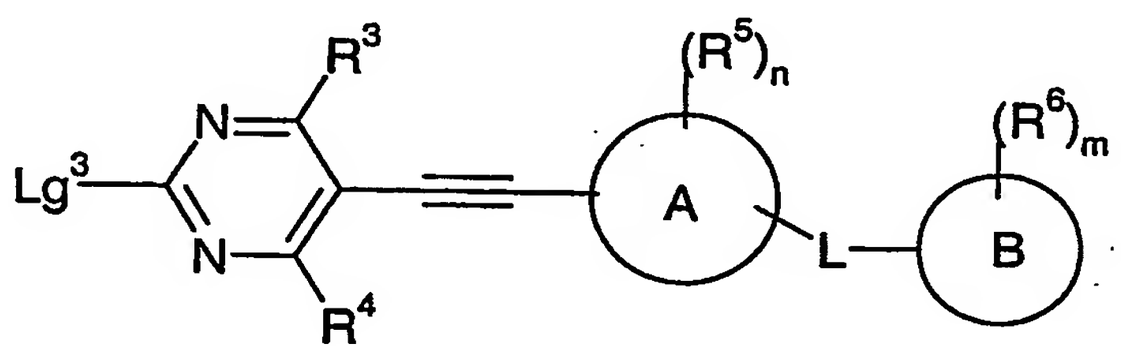


XV

wherein R^6, R^9, m and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (g) The reaction of a compound of the formula XVI:

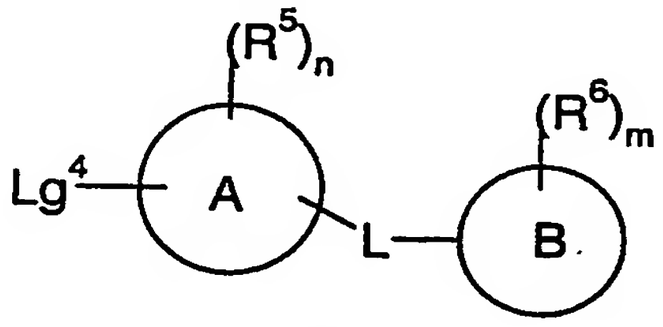


XVI

wherein Lg^3 is a suitable displaceable group for example halogeno (such as fluoro, chloro, bromo or iodo), methyl sulfonyl, methylthio or aryloxy (such as phenoxy) and R^3, R^4, R^5, R^6, n, m, A, B and L have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula HNR^1R^2, wherein R^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

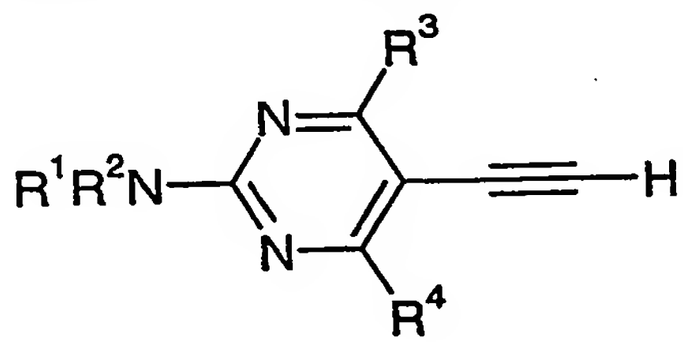
or

Process (h) The reaction of a compound of the formula XVII:



XVII

wherein Lg^4 is a suitable displaceable group for example halogeno (such as chloro, bromo or iodo) or a sulfonyloxy group (such as trifluoromethylsulfonyloxy) and R^5, R^6, n, m, A, B and L have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an alkyne of the formula XVIII:

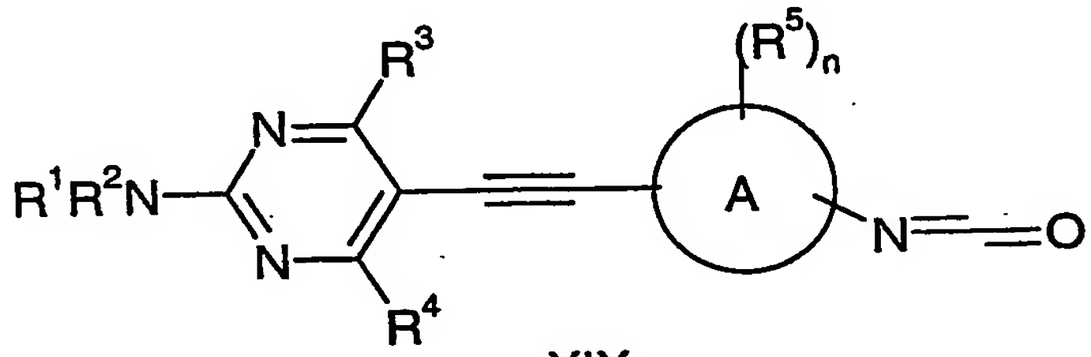


XVIII

wherein R^1, R^2, R^3 and R^4 have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

Process (i) For compounds of the formula I wherein L is $N(H)CON(R^9)$, the reaction of an isocyanate of the formula XIX:

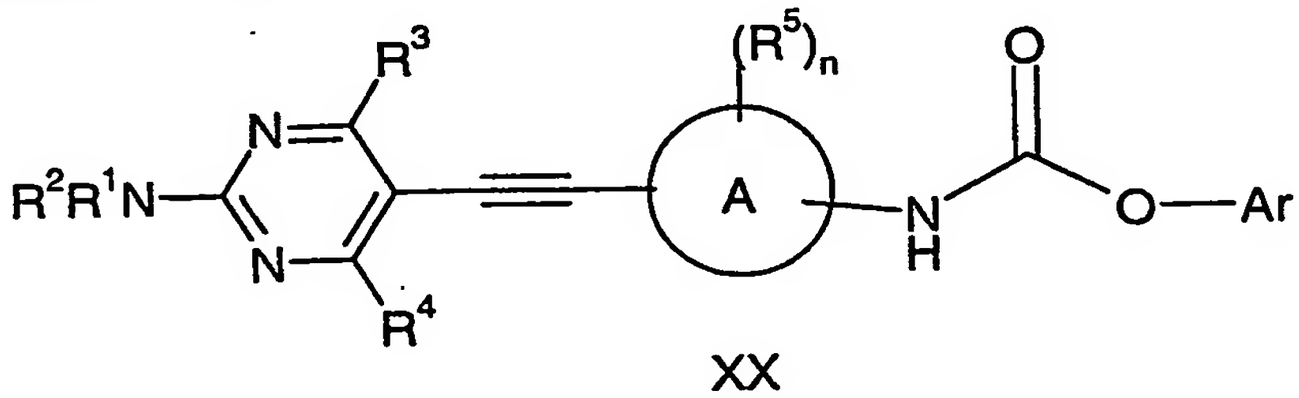


XIX

wherein R^1, R^2, R^3, R^4, R^5, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula XV as defined above;

or

Process (j) For compounds of the formula I wherein L is $N(H)CON(R^9)$, the reaction of a compound of the formula XX:



XX

wherein Ar is a suitable aryl group, for example phenyl, and R^1, R^2, R^3, R^4, R^5, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula XV as defined above.

Reaction Conditions for Process (a)

The reaction of process (a) is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as dichloromethane, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an amine such as pyridine or a dipolar aprotic solvent such as N,N-dimethylformamide or N,N-dimethylacetamide. The reaction is conveniently carried out at a temperature in the range, for example, from ambient temperature to about 60°C, preferably at or near ambient temperature.

Reaction Conditions for Process (b)

The reaction of process (b) is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as pyridine or a trialkylamine (such as triethylamine or diisopropylethylamine).

The reaction of process (b) is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxane or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from ambient temperature to about 120°C, preferably from about 80°C to about 100°C.

Conveniently, this reaction may also be performed by heating the reactants in a sealed vessel using a suitable heating apparatus such as a microwave heater.

Reaction Conditions for Process (c)

The reaction of process (c) is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as pyridine or a trialkylamine (such as triethylamine or diisopropylethylamine) or, for example, an alkali or alkaline earth metal carbonate such as sodium carbonate or potassium carbonate.

The reaction of process (c) is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as dichloromethane, chloroform or carbon tetrachloride or an ether such as tetrahydrofuran or 1,4-dioxane. The reaction is conveniently carried out at a temperature in the range, for example, from about -10°C to about 30°C, preferably at or near 0°C.

Reaction Conditions for Process (d)

When Lg^2 is hydroxy, the reaction of process (d) is conveniently carried out in the presence of a suitable coupling agent. A suitable coupling agent is, for example, a suitable peptide coupling agent, for example O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or a suitable carbodiimide such as dicyclohexylcarbodiimide (DCC) or carbonyldiimidazole (CDI), optionally in the presence of a catalyst such as dimethylaminopyridine or hydroxybenzotriazole.

When Lg^2 is any suitable displaceable group as described above, the reaction of process (d) may conveniently be carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, diisopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene. Another suitable base is, for example, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, caesium carbonate or calcium carbonate.

The reaction of process (d) is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ester such as ethyl acetate, a halogenated solvent such as dichloromethane, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from about 0°C to about 120°C, preferably at or near ambient temperature.

Reaction Conditions for Process (e)

The reaction of process (e) is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as pyridine or a trialkylamine (such as triethylamine or diisopropylethylamine).

The reaction of process (e) is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxane or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from ambient temperature to about 120°C, preferably from about 100°C to about 120°C.

Conveniently, this reaction may also be performed by heating the reactants in a sealed vessel using a suitable heating apparatus such as a microwave heater.

Reaction Conditions for Process (f)

The reaction of process (f) is conveniently carried out under the conditions as described above for process (d).

Reaction Conditions for Process (g)

The reaction of process (g) is conveniently carried out in the presence of a catalytic amount of a suitable acid. A suitable acid is, for example, hydrogen chloride.

The reaction of process (g) may conveniently be carried out in the absence or the presence of a suitable inert solvent or diluent. A suitable inert solvent or diluent, when used, is for example an alcohol such as ethanol, isopropanol or butanol or a dipolar aprotic solvent such as acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from ambient temperature to about 120°C, preferably from about 80°C to about 90°C.

Reaction Conditions for Process (h)

The reaction of process (h) is conveniently carried out in the presence of a suitable palladium catalyst, optionally in combination with a suitable copper catalyst. A suitable palladium catalyst is, for example, bis(triphenylphosphine)palladium dichloride, [1,1'-bis(diphenylphosphino)ferrocene] palladium dichloride or tetrakis(triphenylphosphine)palladium(0). A suitable copper catalyst is, for example, copper (I) iodide.

The reaction of process (h) is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base, such as trialkylamine (for example triethylamine) or tetramethylguanidine.

The reaction of process (h) may conveniently be carried out in the absence or the presence of a suitable inert solvent or diluent, for example an ester such as ethyl acetate, an ether such as tetrahydrofuran or 1,4-dioxane or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a temperature in the range, for example, from about -20°C to about 100°C.

Reaction Conditions for Process (i)

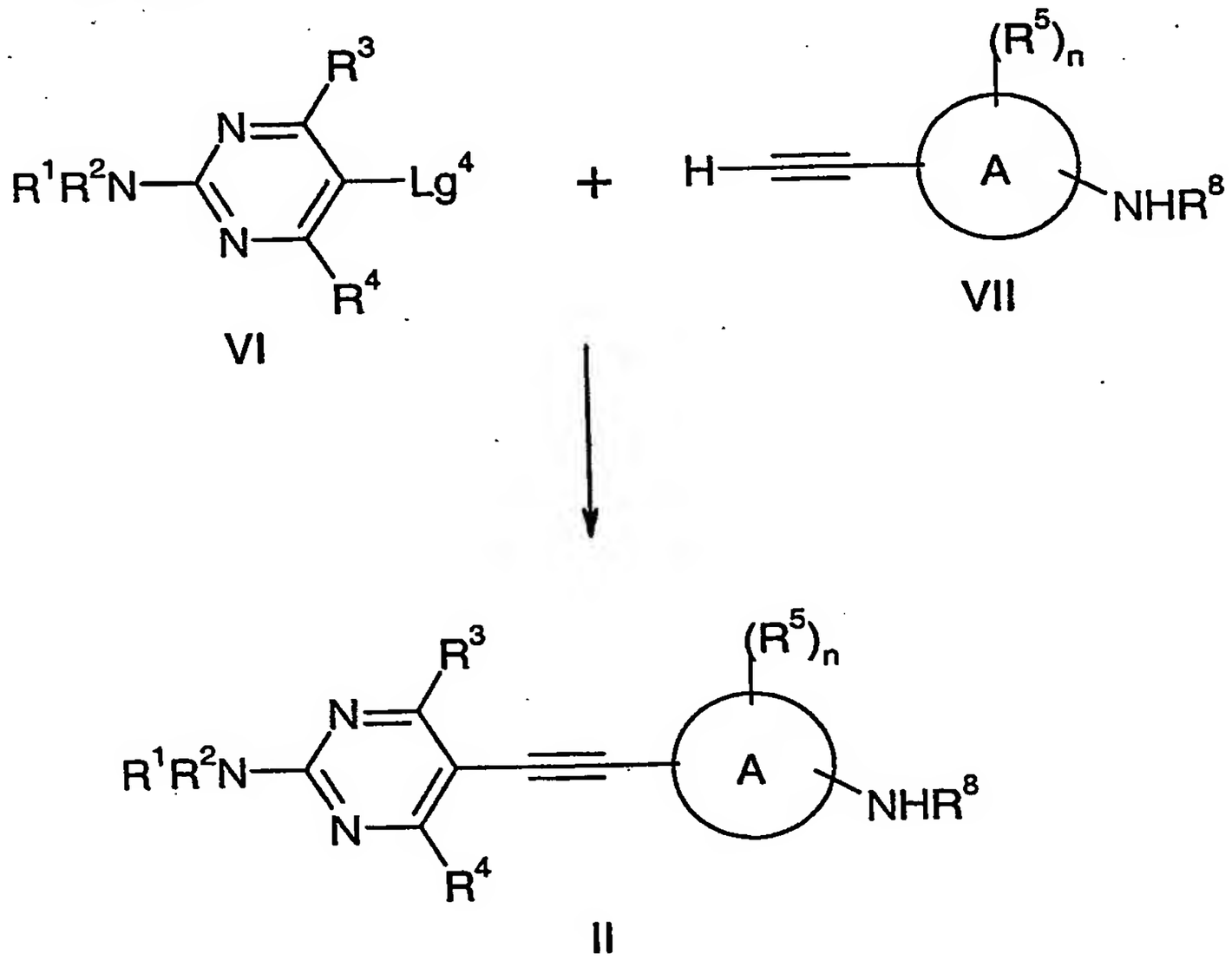
The reaction of process (i) is conveniently carried out under the conditions as described above for process (a).

Reaction Conditions for Process (j)

The reaction of process (j) is conveniently carried out under the conditions as described above for process (b).

Starting Materials for Process (a)

Compounds of the formula II may be obtained by conventional procedures. For example, compounds of the formula II may be obtained by reaction of a pyrimidine of the formula VI with an alkyne of the formula VII as illustrated in *Reaction Scheme 1*:

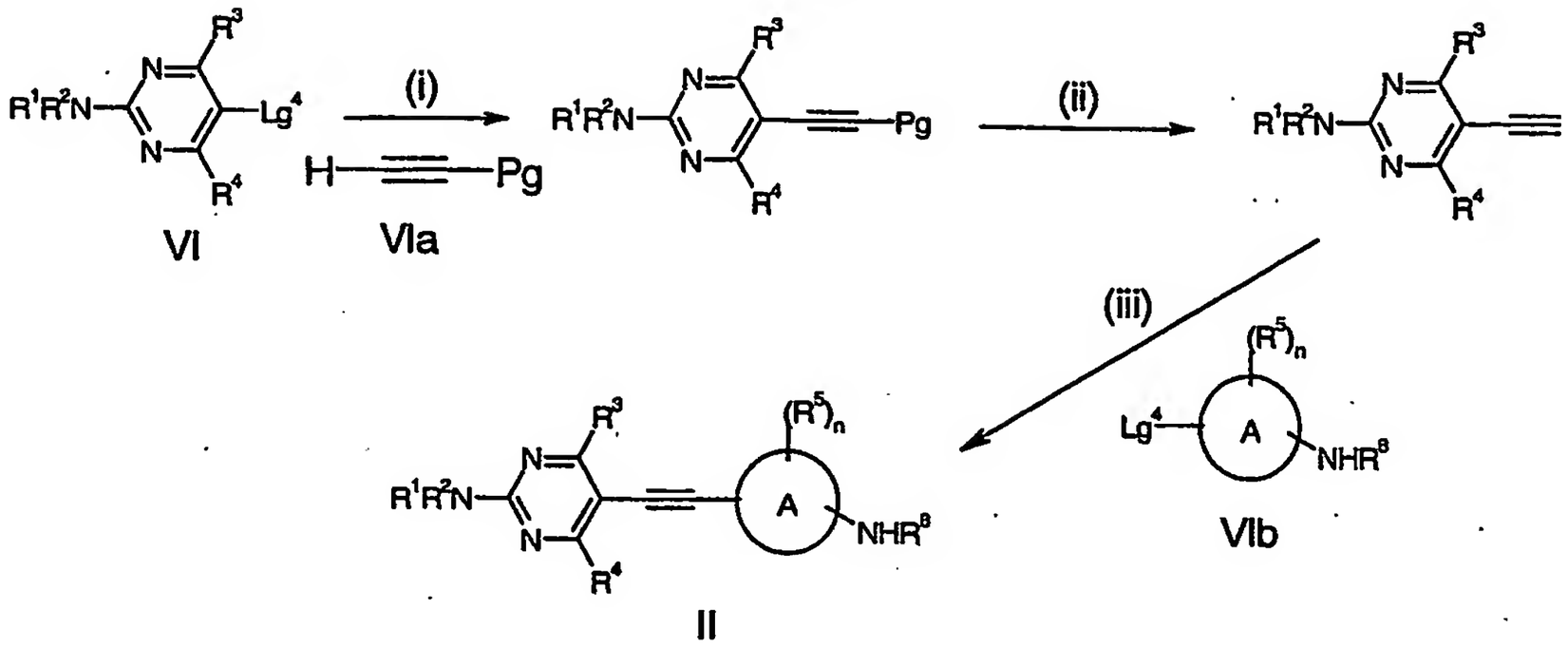


Reaction Scheme 1

wherein Lg^4 is a suitable displaceable group as described above and R^1, R^2, R^3, R^4, R^5, R^8, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary.

The reaction of *Reaction Scheme 1* is conveniently carried out under the conditions as described above for process (h).

Alternatively, compounds of the formula II may be obtained by reaction of a pyrimidine of the formula VI with a protected alkyne of the formula VIa and then with an amine of the formula VIb as illustrated in *Reaction Scheme 2*:

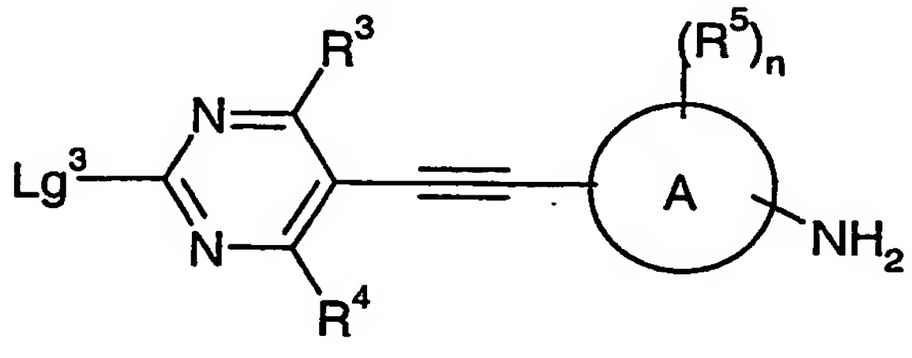


Reaction Scheme 2

wherein Lg^4 in the compounds of the formulae VI and VIb are each a suitable displaceable group as described above, Pg is a suitable protecting group, for example a trialkylsilyl group, such as trimethylsilyl or tert-butyldimethylsilyl or $Me_2(OH)C$- and R^1, R^2, R^3, R^4, R^5, R^8, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary.

Step (i) of *Reaction Scheme 2* is the coupling of a protected alkyne of the formula VIa to a pyrimidine of the formula VI. Step (i) is carried out under conditions as described above for process (h). Step (ii) of *Reaction Scheme 2* is the deprotection of the alkyne under basic or acidic conditions to provide an unprotected alkyne. A person skilled in the art would readily be able to select the appropriate conditions for deprotection in step (ii). Step (iii) of *Reaction Scheme 2* is the coupling of the alkyne to an amine of the formula VIb. Step (iii) of *Reaction Scheme 2* is carried out under conditions as described above for process (h).

Alternatively, compounds of the formula II may be obtained by reaction of a compound of the formula VIc, wherein Lg^3 is a suitable displaceable group as described above and R^3, R^4, R^5, R^8, n and A have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula HNR^1R^2 using reaction conditions as described above for process (g).



VIc

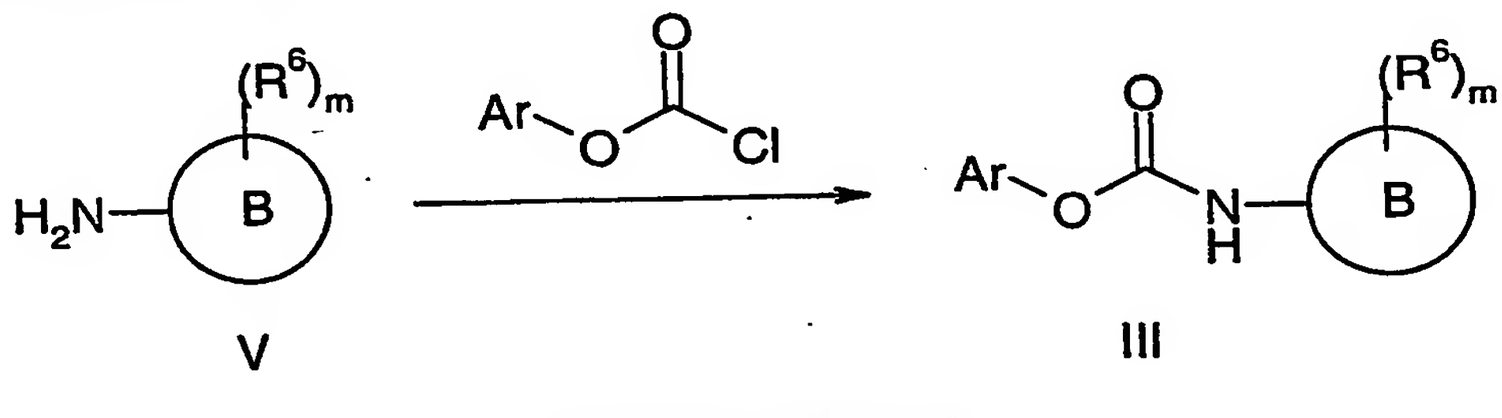
The starting materials of the formulae VI, VII, VIa, VIb and VIc and the amine HNR^1R^2 are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Isocyanates of the formula IV are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art. For example, as the skilled person would appreciate, the isocyanates can conveniently be prepared from the corresponding acids or acid chlorides via a Curtis reaction with for example azide or diphenylphosphoryl azide. Alternatively, the isocyanates can conveniently be prepared by reaction of the corresponding amine with phosgene or a phosgene equivalent, for example triphosgene, diphosgene or N,N'-carbonyldiimidazole (March J., Adv. Org. Chem., 4th edition, 1992, page 1290, Wiley Interscience).

Starting Materials for Process (b)

Compounds of the formula II may be obtained by conventional procedures as discussed above.

Aryl carbamates of the formula III are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art. For example, the aryl carbamates can be prepared by reaction of an amine of the formula V with an arylchloroformate as illustrated in *Reaction Scheme 3*:



V III

Reaction Scheme 3

wherein R^6, m, B and Ar have any of the meanings defined hereinbefore except that any functional group is protected if necessary.

The reaction of *Reaction Scheme 3* is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as pyridine or a trialkylamine (such as triethylamine).

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ether such as tetrahydrofuran or 1,4-dioxane. The reaction is conveniently carried out at a temperature in the range, for example, from about -20°C to about 100°C, preferably at or near 0°C.

The starting material of the formula V and the arylchloroformate are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Starting Materials for Process (c)

Compounds of the formula II may be obtained by conventional procedures as discussed above.

Compounds of the formula XI are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Starting Materials for Process (d)

Compounds of the formula II may be obtained by conventional procedures as discussed above.

Compounds of formula IX are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Starting Materials for Process (e)

Compounds of the formula II may be obtained by conventional procedures as discussed above.

Trichloroacetylamines of the formula XIII are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Starting Materials for Process (f)

Compounds of the formula XIV may be obtained by conventional procedures as discussed above.

Amines of the formula XV are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Starting Materials for Process (g)

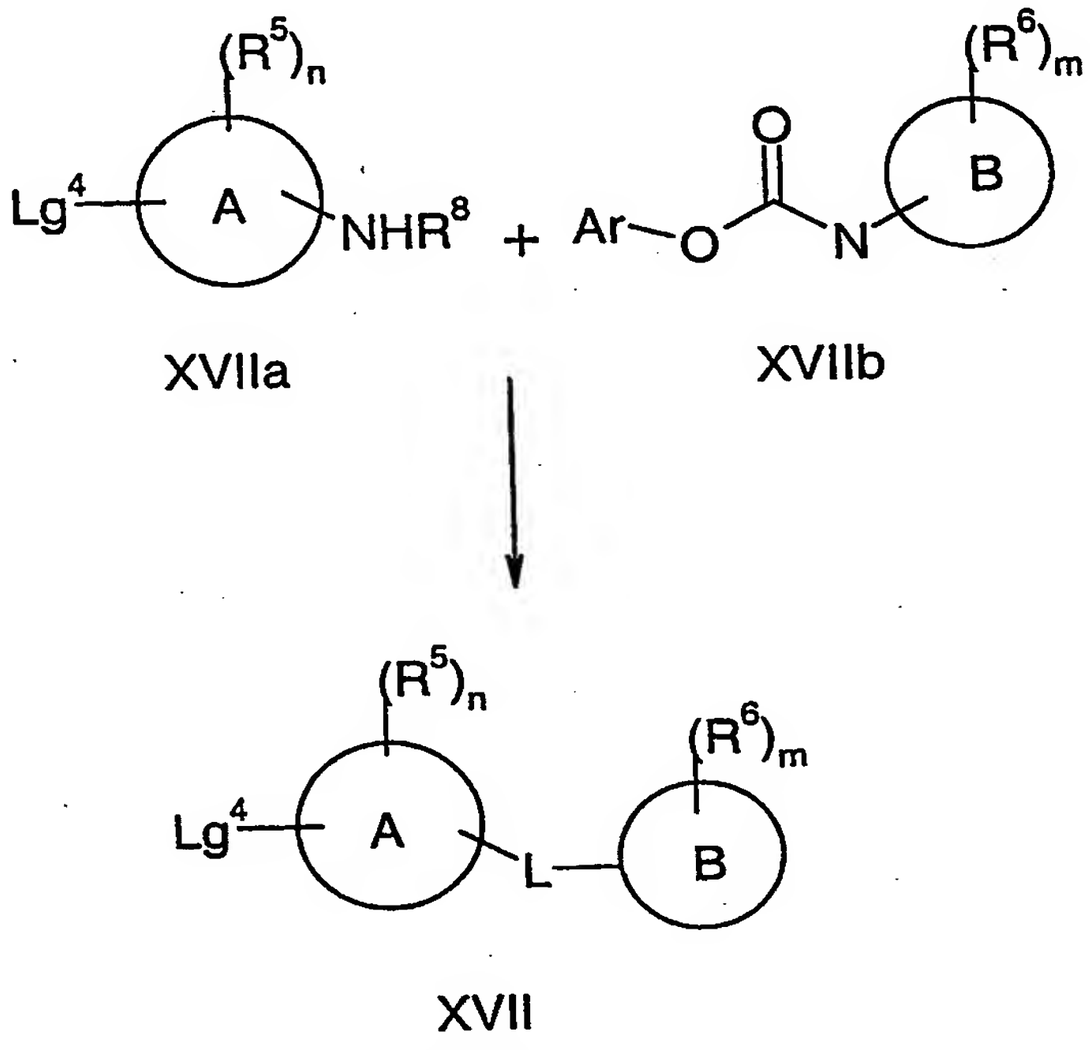
As the skilled person would appreciate, compounds of the formula XVI can be prepared using similar processes to those described above using the appropriate starting materials, for example wherein the starting materials carry an, optionally protected, group Lg^3 in place of the $-NR^1R^2$ group.

Amines of the formula HNR^1R^2 are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Starting Materials for Process (h)

Compounds of formula XVII are commercially available or they are known in the literature, or as the skilled person would appreciate they can be prepared using similar

processes to those described above using the appropriate starting materials. For example, compounds of the formula XVII wherein L is $N(R^8)CON(H)$ may conveniently be obtained by reaction of an amine of the formula XVIIa with an aryl carbamate of the formula XVIIb as illustrated in *Reaction Scheme 4*:



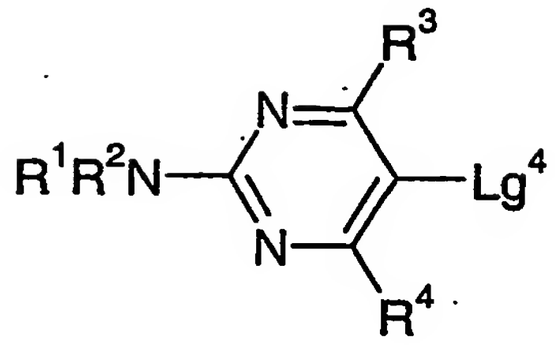
Reaction Scheme 4

wherein Lg^4 is a suitable displaceable group as described above, L is $N(R^8)CON(H)$ and R^5, R^6, R^8, n, m, A and B have any of the meanings defined hereinbefore except that any functional group is protected if necessary.

The reaction of *Reaction Scheme 4* is conveniently carried out under the conditions as described above for process (b).

The starting materials of the formulae XVIIa and XVIIb are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Alkynes of the formula XVIII are commercially available or as the skilled person would appreciate they can be prepared using similar processes to those described above using the appropriate starting materials. For example, compounds of the formula XVIII may conveniently be obtained by reaction of a pyrimidine of the formula XVIIIa:



XVIIIa

wherein Lg^4 is a suitable displaceable group as described above and R^1, R^2, R^3 and R^4 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with trimethylsilylacetylene or 2-methyl-3-butyn-2-ol conveniently under the conditions as described above for process (h), followed by the removal of the protecting group using standard procedures known in the art.

Starting Materials for Process (i)

As the skilled person would appreciate, isocyanates of the formula XIX can conveniently be prepared from the corresponding acids or acid chlorides via a Curtis reaction for example with azide or diphenylphosphoryl azide. Alternatively, the isocyanates can conveniently be prepared by reaction of the corresponding amine with phosgene or a phosgene equivalent, for example triphosgene, diphosgene or N,N'-carbonyldiimidazole (March J., Adv. Org. Chem., 4th edition, 1992, page 1290, Wiley Interscience).

Amines of the formula XV are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Starting Materials for Process (j)

Compounds of formula XX are commercially available or they are known in the literature, or as the skilled person would appreciate they can be prepared using similar processes to those described above using the appropriate starting materials.

Amines of the formula XV are commercially available or they are known in the literature, or they can be prepared by standard processes known in the art.

Compounds of the formula I can be converted into further compounds of the formula I using standard procedures conventional in the art.

Examples of the types of conversion reactions that may be used include introduction of a substituent by means of an aromatic substitution reaction or of a nucleophilic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art.

Particular examples of aromatic substitution reactions include the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under

Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of nucleophilic substitution reactions include the introduction of an alkoxy group or of a monoalkylamino group, a dialkyamino group or a N-containing heterocycle using standard conditions. Particular examples of reduction reactions include the reduction of a carbonyl group to a hydroxy group with sodium borohydride or of a nitro group to an amino group by catalytic hydrogenation with a nickel catalyst or by treatment with iron in the presence of hydrochloric acid with heating.

An example of a suitable conversion reaction is the conversion of a carbamate compound of the formula I wherein R^1, R^2, R^3, R^4, R^5, n and A are as defined in claim 1, L is N(H)C(O)-O- and B is an optionally substituted phenyl group to a compound of the formula I wherein L is N(H)C(O)N(H) and R^1, R^2, R^3, R^4, R^5, n, B and A are as defined in claim 1. Such a conversion may be achieved using standard procedures, for example by reaction of the carbamate with an appropriate amine, for example under conditions as described above for process (b).

Another example of a suitable conversion reaction is the conversion of a compound of the formula I wherein R^2, R^3, R^4, R^5, R^6, n, m, A, B and L are as defined in claim 1 and R^1 and/or R^2 is H to a compound of the formula I wherein R^1 and/or R^2 is, for example, an optionally substituted (1-6C)alkoxycarbonyl group. Such a conversion may be achieved using standard procedures, for example by substitution of one or both of the hydrogen atoms R^1 and/or R^2 for a desired, optionally substituted (1-6C)alkoxycarbonyl group.

Certain compounds of Formula I are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula I and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

Isomers may be resolved or separated by conventional techniques, e.g. chromatography or fractional crystallisation. Enantiomers may be isolated by separation of a racemic or other mixture of the compounds using conventional techniques (e.g. chiral High Performance Liquid Chromatography (HPLC)). Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica) or may be made with achiral starting materials and chiral reagents. All stereoisomers are included within the scope of the invention.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

It will also be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group

by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulfinyl or alkylsulfonyl.

It is believed that certain intermediate compounds of Formulae II, XIV, XVI, XIX, XX and VIc are novel and are herein claimed as another aspect of the present invention.

Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as Tie2 inhibitors in vitro and as inhibitors of Tie2 autophosphorylation in whole cells.

a. In vitro receptor tyrosine kinase inhibition assay

To test for inhibition of Tie2 receptor tyrosine kinase, compounds are evaluated in a non-cell based protein kinase assay by their ability to inhibit the protein kinase enzyme phosphorylation of a tyrosine containing polypeptide substrate in an ELISA based microtitre plate assay. In this particular case, the assay was to determine the IC_{50}, for three different recombinant human tyrosine kinases Tie2, KDR and Flt.

To facilitate production of the tyrosine kinases, recombinant receptor genes were produced using standard molecular biology cloning and mutagenesis techniques. These recombinant proteins fragments encoded within these genes consist of only the intracellular portion C-terminal portion of the respective receptor, within which is found the kinase domain. The recombinant genes encoding the kinase domain containing fragments were cloned and expressed in standard baculovirus/Sf21 system (or alternative equivalent).

Lysates were prepared from the host insect cells following protein expression by treatment with ice-cold lysis buffer (20mM N-2-hydroxyethylpiperizine-N'-2-ethanesulfonic acid (HEPES) pH7.5, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1.5 mM $MgCl_2$, 1 mM ethylene glycol-bis (β-aminoethyl ether) N',N',N',N'- tetraacetic acid (EGTA), plus protease inhibitors and then cleared by centrifugation.
Tie2, KDR and Flt1 lysates were stored in aliquots at -80 °C.

Constitutive kinase activity of these recombinant proteins was determined by their ability to phosphorylate a synthetic peptide (made up of a random co-polymer of Glutamic Acid, Alanine and Tyrosine in the ratio of 6:3:1). Specifically, Nunc Maxisorb™ 96-well immunoplates were coated with 100 microlitres of synthetic peptide Sigma P3899 (1mg/ml stock solution in PBS diluted 1:500 in PBS prior to plate coating) and incubated at 4 °C

overnight. Plates were washed in 50 mM HEPES pH 7.4 at room temperature to remove any excess unbound synthetic peptide.

Tie2, KDR or Flt1 activities were assessed by incubation of the appropriate freshly diluted lysates (1:200, 1:400 and 1:1000 respectively) in peptide coated plates for 60 minutes (Tie2) or 20 minutes for (KDR, Flt) at room temperature in100 mM HEPES pH 7.4, adenosine trisphosphate (ATP) at 5 micromolar (or Km concentration for the respective enzyme, 10 mM $MnCl_2$, 0.1 mM Na_3VO_4, 0.2 mM DL-dithiothreitol (DTT), 0.1% Triton X-100 together with the test compound(s) in dissolved in DMSO (final concentration of 2.5%) with final compound concentrations ranging from 0.05 micromolar –100 micromolar. Reactions were terminated by the removal of the liquid components of the assay followed by washing of the plates with PBS-T (phosphate buffered saline with 0.5% Tween 20) or an alternative equivalent wash buffer.

The immobilised phospho-peptide product of the reaction was detected by immunological methods. Firstly, plates were incubated for 4 hours at room temperature with murine monoclonal anti-phosphotyrosin –HRP (Horseradish Peroxidase) conjugated antibodies (4G10 from Upstate Biotechnology UBI 16-105). Following extensive washing with PBS-T, HRP activity in each well of the plate was measured colorimetrically using 22'-Azino-di-[3-ethylbenzthiazoline sulfonate (6)] diammonium salt crystals ABTS (Sigma P4922 – prepared as per manufactures instructions) as a substrate incubated for 30-45 minutes to allow colour development, before 100ul of 1M H_2SO_4 was added to stop the reaction.

Quantification of colour development and thus enzyme activity was achieved by the measurement of absorbance at 405nm on a Molecular Devices ThermoMax microplate reader. Kinase inhibition for a given compound was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of phosphorylation in this assay. The range of phosphorylation was calculated from the positive (vehicle plus ATP) and negative (vehicle minus ATP) control values.

b. Cellular Tie2 autophosphorylation assay

This assay is based on measuring the ability of compounds to inhibit autophosphorylation of the Tie2 receptor, which normally leads to the production of "activated" receptor that in turn initiates the particular signal transduction pathways associated with the receptor function.

Autophosphorylation can be achieved by a number of means. It is known that expression of recombinant kinase domains in baculoviral systems can lead to the production of phosphorylated and activated receptor. It is also reported that over expression of receptors in

recombinant cell lines can itself lead to receptor autophosphorylation in the absence of the ligand (Heldin C-H. 1995 Cell: 80, 213-223; Blume-J. P, Hunter T., 2001 Nature: 411, 355-65). Furthermore, there are numerous literature examples in which chimaeric receptors have been constructed. In these cases the natural, external cell surface domain of the receptor has been replaced with that of a domain which is known to be readily dimerised via the addition of the appropriate ligand (e.g. TrkA-Tie2/NGF ligand (Marron, M.B. et al., 2000 Journal of Biological Chemistry: 275:39741-39746) or C-fms-Tie-1/CSF-1 ligand (Kontos, C.D. et al., 2002 Molecular and Cellular Biology: 22, 1704-1713). Thus when the chimaeric receptor expressed in a host cell line and the respective ligand is added, this induces autophosphorylation of the chimeric receptor's kinase domain. This approach has the advantage of often allowing a known (and often easily obtained) ligand to be used instead of having to identify and isolate the natural ligand for each receptor of interest.

Naturally if the ligand is available one can use natural cell lines or primary cells that are known to express the receptor of choice and simply stimulate with ligand to achieve ligand induced phosphorylation. The ability of compounds to inhibit autophosphorylation of the Tie2 receptor, which is expressed for example in EA.hy926/B3 cells (supplied by J. McLean/ B. Tuchi, Univ.of N. Carolina at Chapel Hill, CB- 4100, 300 Bynum Hall, Chapel Hill, N.C. 27599-41000, USA) or primary HUVEC (human umbilical vein endothelial cells - available from various commercial sources), can measured by this assay.

CHO cells stably transfected with Tie2 were grown in the appropriate tissue culture media plus 10% foetal calf serum (FCS) for 3 days in 96 well plates starting with an initial seeding density of $3x10^4$ cells per well. On the fourth day the media was removed and replaced with 250uL of the test compound dilution (compound dilutions made in culture media plus 1% FCS keeping the DMSO concentration below 0.8%). After 45 minutes at 37°C the cells were cooled on ice, washed with 200uL PBS/A containing 1mM $NaVO_4$, after which 100uL of lysis buffer (20 mM Tris pH 7.6, 150 mM NaCl, 50 mM NaF, 0.1 % SDS, 1% NP40, 0.5 % DOC, 1 mM orthovanadate, 1 mM EDTA, 1 mM PMSF, 30 µl / ml Aprotinin, 10 µg/ml Pepstatin, 10 µg/ml Leupeptin) was added to the cells and left on ice for 5 minutes. The lysates were transferred to R&D Systems anti-Tie2 antibody coated 96 well plates and gently shaken for two hours at room temperature.

Wells were washed four times with 200uL R&D Systems wash buffer before adding 200uL anti-phospho-Tie2 antibody (Cell Signalling Technologies) (1:1000 dilution in PBS/A plus 0.05% polysorbate) per well. Plates were gently shaken at room temperature for two

hours. Wells were washed four times with 200uL R&D Systems wash buffer before adding 200uL goat anti-rabbit-POD (HRP) antibody (Dako) (1:2000 dilution in PBS/A plus 0.05% polysorbate) per well. Plates were incubated at room temperature for two hours.

Wells were washed four times with 200uL R&D Systems wash buffer before adding 200uL R&D Systems colour reagent to each well followed by incubation in the dark for 30 minutes. The colour reaction was stopped by addition of 50uL R&D Systems stopping reagent per well. Colour development across plates was determined using a plate reader at 450nm wavelength. Inhibition of phosphorylation for each test compound dilution series was determined from which IC_{50} values were calculated by standard methods using appropriate controls samples as reference and appropriate controls.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a) and (b):-

Test(a):- IC_{50} in the range, for example, < 100μM;

Test (b):- IC_{50} in the range, for example, < 50μM;

By way of example, Table A illustrates the activity of representative compounds according to the invention. Column 2 of Table A shows IC_{50} data from Test (a) for the inhibition of Tie2 receptor tyrosine kinase *in vitro* and column 3 shows IC_{50} data from Test (b) for the inhibition of autophosphorylation of Tie2 receptor tyrosine kinase.

Table A

Example Number	IC_{50} (μM) Test (a): Inhibition of Tie2 receptor tyrosine kinase *in vitro*	IC_{50} (μM) Test (b): Inhibition of autophosphorylation of Tie2 receptor tyrosine kinase
19	19.871	0.337
33	5.700	2.592
48	74.949	3.287

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the Formula I, or a pharmaceutically acceptable

salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however

preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

The compounds according to the present invention as defined herein are of interest for, amongst other things, their antiangiogenic effect. The compounds of the invention are expected to be useful in the treatment or prophylaxis of a wide range of disease states associated with undesirable or pathological angiogenesis, including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, lymphoedema, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation. Cancer may affect any tissue and includes leukaemia, multiple myeloma and lymphoma. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin.

We believe that the antiangiogenic properties of the compounds according to the present invention arise from their Tie2 receptor tyrosine kinase inhibitory properties. Accordingly, the compounds of the present invention are expected be useful to produce a Tie2 inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention may be used to produce an antiangiogenic effect mediated alone or in part by the inhibition of Tie2 receptor tyrosine kinase.

More particularly the compounds of the invention are expected to inhibit any form of cancer associated with Tie2. For example, the growth of those primary and recurrent solid tumours which are associated with Tie2, especially those tumours which are significantly dependent on Tie2 receptor tyrosine kinase for their growth and spread.

According to a further aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore, for use as a medicament.

According to another aspect of the invention, there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore, in the manufacture of a medicament for use as a Tie2 receptor tyrosine kinase inhibitor in a warm-blooded animal such as man.

According to another aspect of the invention, there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore, in the

manufacture of a medicament for use in the production of an anti-angiogenic effect in a warm-blooded animal such as man.

According to another aspect of the invention, there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of cancers in a warm-blooded animal such as man.

According to another aspect of the invention, there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a cancer selected from leukaemia, breast, lung, colon, rectal, stomach, prostate, bladder, pancreas, ovarian, lymphoma, testicular, neuroblastoma, hepatic, bile duct, renal cell, uterine, thyroid and skin cancer in a warm-blooded animal such as man.

According to another aspect of the invention there is provided a method of inhibiting Tie2 receptor tyrosine kinase in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to another aspect of the invention there is provided a method for producing an anti-angiogenic effect in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to another aspect of the invention there is provided a method of treating cancers in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to another aspect of the invention there is provided a method of treating a cancer selected from leukaemia, breast, lung, colon, rectal, stomach, prostate, bladder, pancreas, ovarian, lymphoma, testicular, neuroblastoma, hepatic, bile duct, renal cell, uterine, thyroid or skin cancer, in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to another aspect of the invention there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore, for use in inhibiting Tie2 receptor tyrosine kinase in a warm-blooded animal, such as man.

According to another aspect of the invention there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore, for use in producing an anti-angiogenic effect in a warm-blooded animal, such as man.

According to another aspect of the invention there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore, for use in the treatment of cancer.

According to another aspect of the invention there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore, for use in the treatment of a cancer selected from leukaemia, breast, lung, colon, rectal, stomach, prostate, bladder, pancreas, ovarian, lymphoma, testicular, neuroblastoma, hepatic, bile duct, renal cell, uterine, thyroid or skin cancer.

As hereinbefore mentioned it is further expected that a compound of the present invention will possess activity against other diseases mediated by undesirable or pathological angiogenesis including psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, lymphoedema, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation.

The anti-angiogenic activity defined herein may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the anti-angiogenic treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:

(i) anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred

antimetabolites disclosed in European Patent Application No. 562734 such as (2S)-2-{o-fluoro-p-[N-{2,7-dimethyl-4-oxo-3,4-dihydroquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]benzamido}-4-(tetrazol-5-yl)butyric acid); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(iii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrazole, vorazole and exemestane) and inhibitors of 5 α-reductase such as finasteride;

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies, farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example the EGFR tyrosine kinase inhibitors N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (CP 358774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents that work by different mechanisms to those defined hereinbefore, such as those which inhibit vascular endothelial growth factor such as the compounds disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and those that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) biotherapeutic therapeutic approaches for example those which use peptides or proteins (such as antibodies or soluble external receptor domain constructions) which either sequest receptor ligands, block ligand binding to receptor or decrease receptor signalling (e.g. due to enhanced receptor degradation or lowered expression levels)

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the Formula I as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

In addition to their use in therapeutic medicine, the compounds of Formula I and their pharmaceutically acceptable salts, are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of anti-angiogenic activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C;

(ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600–4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60 °C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and / or analytical LC-MS, and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulfoxide (DMSO-d_6) as solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in volume:volume (v/v) terms; and

(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is MH^+;

(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulfur atom have not been resolved;

(xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xvi) the following abbreviations have been used:

AcOH	Acetic acid
AIBN	2,2'-Azobisisobutyronitrile
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMA	*N,N*-Dimethylacetamide
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride

dppf	1,1'-Bis(diphenylphosphino)ferrocene
EtOAc	Ethylacetate
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
^{i}PrMgCl	Isopropylmagnesium chloride
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl) amide
m-CPBA	*meta*-Chloroperbenzoic acid
MeOH	Methanol
MeCN	Acetonitrile
MCX	Mixed cation exchange resin
MTBE	Methyl *tert*-butyl ether
LCMS	Liquid Chromatograpy – Mass Spectrometry
NMP	1-Methyl-2-pyrrolidinone
$POCl_3$	Phosphorus oxychloride
RPHPLC	Reversed phase high peformance liquid chromatography
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

xvii) where a synthesis is described as leading to an acid addition salt (e.g. HCl salt), no comment is made on the stoichiometry of this salt. Unless otherwise stated, all NMR data is reported on free-base material, with isolated salts converted to the free-base form prior to characterisation.

Example 1

***N*-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-*N'*-[2-fluoro-5-(trifluoromethyl)phenyl]urea**

5-[(3-aminophenyl)ethynyl]pyrimidin-2-amine (105 mg) was stirred in THF and 2-fluoro-5-trifluoromethylphenyl isocyanate (123 mg) was added dropwise. After 30 min, methylethylenediamine-polystyrene (200 mg) was added and stirring continued for 30 min. The reaction mixture was filtered and concentrated to give a grey solid which was purified by flash chromatography on silica using 0-10% MeOH in DCM as eluent to give the title compound as a yellow solid (166 mg, 80%);

^{1}H NMR (DMSO-d_6) 7.13 (bs, 2H), 7.16-7.19 (m, 1H), 7.32-7.44 (m, 3H), 7.50-7.54 (m, 1H), 7.80 (bs, 1H), 8.47 (s, 2H), 8.61-8.64 (m, 1H), 8.94-8.95 (m, 1H), 9.28 (s, 1H);
MS m/e MH^+ 416.

Preparation of Intermediate 1

5-[(3-aminophenyl)ethynyl]pyrimidin-2-amine

2-Amino-5-iodopyrimidine (2.21 g), bis(triphenylphosphine)palladium dichloride (350 mg) and copper(I) iodide (40 mg) were stirred in DMF (100 mL)-triethylamine (20 mL) and degassed with nitrogen for 10 min. 3-Ethynyl aniline (1.29 g) was added and the mixture heated to 95 °C for 2 hours. The solvent was evaporated and the residue was purified by trituration with DCM (20 mL) to give the title compound as a brown solid (1.25 g, 60%);
^{1}H NMR (DMSO-d_6) 5.21 (bs, 2H), 6.58-6.70 (m, 3H), 7.03-7.07 (m, 3H), 8.40 (s, 2H);
MS m/e MH^+ 211.

Examples 2 to 17 were prepared by an analogous method to Example 1 but purified by trituration from methanol.

Example 2

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[2-(trifluoromethyl)phenyl]urea

Starting Materials: Intermediate 1 and 2-trifluoromethylphenyl isocyanate.
^{1}H NMR (DMSO-d_6) 7.13–7.16 (m, 3H), 7.29–7.35 (m, 3H), 7.64-7.72 (m, 2H), 7.78 (s, 1H), 7.95 (d, 1H), 8.13 (s, 1H), 8.45 (s, 2H), 9.47 (s, 1H);
MS m/e MH^+ 398.

Example 3

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[4-(trifluoromethyl)phenyl]urea

Starting Materials: Intermediate 1 and 4-trifluoromethylphenyl isocyanate.
^{1}H NMR (DMSO-d_6) 7.14–7.17 (m, 3H), 7.32–7.41 (m, 2H), 7.64-7.71 (m, 4H), 7.75 (s, 1H), 8.46 (s, 2H), 8.92 (s, 1H), 9.16 (s, 1H);
MS m/e MH^+ 398.

Example 4

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2-fluorophenyl)urea

Starting Materials: Intermediate 1 and 2-fluorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 7.00–7.08 (m, 1H), 7.14–7.29 (m, 5H), 7.34 (d, 2H), 7.76 (s, 1H), 8.15 (td, 1H), 8.46 (s, 2H), 8.59 (s, 1H), 9.18 (s, 1H);

MS m/e MH^++MeCN 389.

Example 5

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-fluorophenyl)urea

Starting Materials: Intermediate 1 and 3-fluorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 6.81 (td, 1H), 7.12–7.16 (m, 4H); 7.29-7.39 (m, 3H), 7.50 (dt, 1H), 7.74 (d, 1H), 8.46 (s, 2H), 8.85 (s, 1H), 8.96 (s, 1H);

MS m/e MH^++MeCN 389.

Example 6

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(4-fluorophenyl)urea

Starting Materials: Intermediate 1 and 4-fluorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 7.11–7.17 (m, 5H); 7.30-7.38 (m, 2H), 7.46-7.51 (m, 2H), 7.73 (s, 1H), 8.45 (s, 2H), 8.75 (s, 1H), 8.77 (s, 1H);

MS m/e MH^++MeCN 389.

Example 7

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-methoxyphenyl)urea

Starting Materials: Intermediate 1 and 3-methoxyphenyl isocyanate.

^{1}H NMR (DMSO-d_6) 3.76 (s, 3H), 6.58 (dd, 1H), 6.94–6.97 (m, 1H); 7.11-7.23 (m, 5H), 7.30-7.37 (m, 2H), 7.75 (s, 1H), 8.46 (s, 2H), 8.73 (s, 1H), 8.76 (s, 1H);

MS m/e MH^++MeCN 401.

Example 8

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2,5-difluorophenyl)urea

Starting Materials: Intermediate 1 and 2,5-difluorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 6.81–6.89 (m, 1H), 7.14–7.18 (m, 3H), 7.27-7.38 (m, 3H), 7.76 (s, 1H), 8.02-8.08 (m, 1H), 8.46 (s, 2H), 8.81 (s, 1H), 9.25 (s, 1H);

MS m/e MH^++MeCN 407.

Example 9

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-1,3-benzodioxol-5-ylurea

Starting Materials: Intermediate 1 and 3,4-methylenedioxyphenyl isocyanate.

^{1}H NMR (DMSO-d_6) 5.99 (s, 2H), 6.77–6.86 (m, 2H), 7.09–7.13 (m, 3H), 7.21-7.22 (m, 1H), 7.28-7.36 (m, 2H), 7.72 (s, 1H), 8.45 (s, 2H), 8.60 (s, 1H), 8.71 (s, 1H);

MS m/e MH^++MeCN 415.

Example 10

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[3-(trifluoromethyl)phenyl]urea

Starting Materials: Intermediate 1 and 3-trifluoromethylphenyl isocyanate.

^{1}H NMR (DMSO-d_6) 7.14–7.16 (m, 3H), 7.31–7.40 (m, 3H), 7.51-7.61 (m, 2H), 7.77 (s, 1H), 8.05 (s, 1H), 8.46 (s, 2H), 8.91 (s, 1H), 9.10 (s, 1H);

MS m/e MH^++MeCN 439.

Example 11

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2-methoxyphenyl)urea

Starting Materials: Intermediate 1 and 2-methoxyphenyl isocyanate.

^{1}H NMR (DMSO-d_6) 3.90 (s, 3H), 6.89-7.11 (m, 3H), 7.11-7.13 (m, 3H), 7.32-7.34 (m, 2H), 7.77 (s, 1H), 8.14 (dd, 1H), 8.26 (s, 1H), 8.46 (s, 2H), 9.43 (s, 1H);

MS m/e MH^+ 360.

Example 12

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(4-methoxyphenyl)urea

Starting Materials: Intermediate 1 and 4-methoxyphenyl isocyanate.

^{1}H NMR (DMSO-d_6) 3.74 (s, 3H), 6.88–6.90 (m, 2H); 7.09-7.13 (m, 3H), 7.28-7.39 (m, 4H), 7.74 (s, 1H), 8.45 (s, 2H), 8.52 (s, 1H), 8.69 (s, 1H);

MS m/e MH^++MeCN 401.

Example 13

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3,4-difluorophenyl)urea

Starting Materials: Intermediate 1 and 3,4-difluorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 7.13-7.15 (m, 4H), 7.31-7.41 (m, 3H), 7.64-7.73 (m, 2H), 8.45 (s, 2H), 8.86 (s, 1H), 8.95 (s, 1H);

MS m/e MH^++MeCN 407.

Example 14

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-cyanophenyl)urea

Starting Materials: Intermediate 1 and 3-cyanophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 7.14-7.16 (m, 3H), 7.32-7.55 (m, 4H), 7.69-7.75 (m, 2H), 8.00 (s, 1H), 8.46 (s, 2H), 8.96 (s, 1H), 9.08 (s, 1H);

MS m/e MH^+ 355.

Example 15

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-chlorophenyl)urea

Starting Materials: Intermediate 1 and 3-chlorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 7.03-7.06 (m, 1H), 7.13-7.15 (m, 3H), 7.27-7.39 (m, 4H), 7.74-7.75 (m, 2H), 8.46 (s, 2H), 8.87 (s, 1H), 8.95 (s, 1H);

MS m/e MH^++MeCN 405.

Example 16

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-cyclopentylurea

Starting Materials: Intermediate 1 and cyclopentyl isocyanate.

^{1}H NMR (DMSO-d_6) 1.36-1.44 (m, 2H), 1.53-1.68 (m, 4H), 1.81-1.91 (m, 2H), 3.95 (sextet, 1H), 6.21 (d, 1H), 7.02-7.04 (m, 1H), 7.12 (s, 2H), 7.24-7.26 (m, 2H), 7.68 (s, 1H), 8.36 (s, 1H), 8.44 (s, 2H);

MS m/e MH^+ 322.

Example 17

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3,5-difluorophenyl)urea

Starting Materials: Intermediate 1 and 3,5-difluorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 6.77-6.85 (m, 1H), 7.14-7.25 (m, 5H), 7.31-7.40 (m, 2H), 7.74 (s, 1H), 8.46 (s, 2H), 8.96 (s, 1H), 9.14 (s, 1H);

MS m/e MH^++MeCN 407.

Example 18

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-tert-butyl-1,3,4-thiadiazol-2-yl)urea

5-[(3-aminophenyl)ethynyl]pyrimidine-2-amine (Intermediate 1) (50.0 mg), triethylamine (0.04 mL) and phenyl (5-tert-butyl-1,3,4-thiadiazol-2-yl)carbamate (Intermediate 2) (79.0 mg) in THF (2 mL) were irradiated under microwave conditions (CEM explorer, 80°C, 50W) for 20 min. The reaction mixture was concentrated *in vacuo*, purification by flash chromatography on silica using 1-10% MeOH in DCM as eluent gave the title compound as a solid (35 mg, 37%);

^{1}H NMR (DMSO-d_6) 1.38 (s, 9H), 7.08-7.19 (m, 3H), 7.33-7.37 (t, 1H), 7.37-7.45 (m, 1H), 7.75 (s, 1H), 8.43 (s, 2H), 9.10 (bs, 1H), 10.89 (bs, 1H);

MS m/e MH^+ 394.

Intermediate 2

Phenyl (5-tert-butyl-1,3,4-thiadiazol-2-yl)carbamate

Phenylchloroformate (0.6 mL) was added dropwise to 2-amino-5-tert-butyl-1,3,4-thiadiazole (0.5 g) and pyridine (0.51 mL) in THF (40 mL) at 0°C. After 2 hour, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3x 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica using 20-50% EtOAc in isohexane gave the title compound as a yellow solid (0.819 mg, 93%);

^{1}H NMR (DMSO-d_6) 1.38 (s, 9H), 7.22-7.28 (m, 3H), 7.41-7.44 (m, 2H);

MS m/e MH^+ 278.

Intermediates 3 to 7 were prepared by an analogous method to Intermediate 2 using phenylchloroformate and the appropriate heterocyclic amine.

Intermediate 3

Phenyl (3-methylisoxazol-5-yl)carbamate

Starting Materials: Phenylchloroformate and 5-amino-3-methyl isoxazole.

^{1}H NMR (DMSO-d_6) 2.17 (s, 3H), 5.93 (s, 1H), 7.21-7.30 (m, 3H), 7.41-7.46 (m, 2H), 11.79 (bs, 1H);

MS m/e MH^+ 219.

Intermediate 4

Phenyl (5-tert-butylisoxazol-3-yl)carbamate

Starting Materials: Phenylchloroformate and 3-amino-5-*tert*-butylisoxazole.

^{1}H NMR (DMSO-d_6) 1.28 (s, 9H), 6.42 (s, 1H), 7.18-7.26 (m, 3H), 7.39-7.45 (m, 2H), 11.13 (bs, 1H);

MS m/e MH^+ 261.

Intermediate 5

Phenyl [4-(trifluoromethyl)pyridin-2-yl]carbamate

Starting Materials: Phenylchloroformate and 2-amino-4-trifluoromethylpyridine.

^{1}H NMR (DMSO-d_6) 7.22-7.30 (m, 3H), 7.41-7.46 (m, 3H), 8.11 (s, 1H), 8.59-8.61 (d, 1H), 11.23 (bs, 1H);

MS m/e MH^+ 283.

Intermediate 6

Phenyl [3-(acetylamino)phenyl]carbamate

Starting Materials: Phenylchloroformate and 3-aminoacetanilide.

^{1}H NMR (DMSO-d_6) 2.01 (s, 3H), 7.17-7.30 (m, 6H), 7.38-7.44 (m, 2H), 7.77 (s, 1H), 9.90 (bs, 1H), 10.16 (bs, 1H);

MS m/e MH^+ 271.

Intermediate 7

Phenyl (3-methylisothiazol-5-yl)carbamate

Starting Materials: Phenylchloroformate and 3-methyl-5-aminoisothiazole.

^{1}H NMR (DMSO-d_6) 2.30 (s, 3H), 6.68 (s, 1H), 7.25-7.31 (m, 3H), 7.41-7.46 (m, 2H), 11.90 (bs, 1H);

MS m/e MH^+ 235.

Examples 19 and 20 were prepared by an analogous method to Example 18 (using the appropriate starting materials), except purification was by reverse phase HPLC, gradient H_2O:MeCN (0-70%).

Example 19

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(3-methylisoxazol-5-yl)urea

Starting Materials: Intermediate 1 and Intermediate 3.

^{1}H NMR (DMSO-d_6) 2.16 (s, 3H), 5.96 (s, 1H), 7.02-7.18 (m, 3H), 7.28-7.39 (m, 2H), 7.70 (s, 1H), 8.41 (s, 2H), 8.92 (s, 1H), 10.15 (s, 1H);

MS m/e MH^+ 335.

Example 20

N-(3-{[({3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}amino)carbonyl]amino}phenyl)acetamide

Starting Materials: Intermediate 1 and Intermediate 6.

^{1}H NMR (DMSO-d_6) 2.02 (s, 3H), 7.04-7.11 (m, 3H), 7.14-7.18 (m, 3H), 7.28-7.36 (m, 2H), 7.71 (s, 1H), 7.78 (s, 1H), 8.41 (s, 2H), 8.66 (s, 1H), 8.75 (s, 1H), 9.86 (s, 1H);

MS m/e MH^+ 387.

Example 21

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-[4-(trifluoromethyl)pyridin-2-yl]urea

Example 21 was prepared by an analogous method to Example 18 using Intermediate 1 and Intermediate 5. Purification was by trituration with DCM/MeOH.

^{1}H NMR (DMSO-d_6) 7.11 (s, 2H), 7.14-7.19 (d, 1H), 7.31-7.43 (m, 3H), 7.78 (s, 1H), 8.04 (s, 1H), 8.43 (s, 2H), 8.52-8.57 (d, 1H), 9.73 (s, 1H), 9.84 (s, 1H);

MS m/e MH^+ 399.

Example 22

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-tert-butylisoxazol-3-yl)urea

Example 22 was prepared by an analogous method to Example 18 using Intermediate 1 and Intermediate 4. Purification was by trituration with THF.

^{1}H NMR (DMSO-d_6) 1.32 (s, 9H), 6.53 (s, 1H), 7.14-7.18 (m, 3H), 7.31-7.36 (m, 2H), 7.74 (s, 1H), 8.45 (s, 2H), 9.04 (s, 1H), 9.62 (s, 1H);

MS m/e MH^+ 377.

Example 23

Phenyl {3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}carbamate

Example 23 was prepared by an analogous method to Intermediate 2 using Intermediate 1 and phenylchloroformate. Purification was by trituration with DCM.

^{1}H NMR (DMSO-d_6) 7.15 (s, 2H), 7.20-7.32 (m, 4H), 7.36-7.55 (m, 4H), 7.69 (s, 1H), 8.45 (s, 2H), 10.37 (s, 1H);

MS m/e MH^+ 331.

Example 24

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2-oxopiperidin-3-yl)urea

Phenyl {3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}carbamate (Example 23) (50 mg), 3-amino-piperidin-2-one hydrochloride (46 mg) and triethylamine (0.06 mL) in THF (2 mL) were heated at 80°C for 24 hours. The reaction mixture was concentrated *in vacuo* and the solid triturated with water then diethyl ether, dried under vacuum at 60°C to give the title compound as a beige solid (41 mg, 77%);

^{1}H NMR (DMSO-d_6) 1.49-1.62 (m, 1H), 1.71-1.82 (m, 2H), 2.16-2.28 (m, 1H), 3.10-3.18 (m, 2H), 3.95-4.04 (m, 1H), 6.42-6.48 (d, 2H), 6.98-7.04 (m, 1H), 7.09 (s, 2H), 7.20-7.31 (m, 2H), 7.65 (s, 2H), 8.41 (s, 2H), 8.85 (s, 1H);

MS m/e MH^+ 351.

Example 25

N-(5-tert-butylisoxazol-3-yl)-N'-(3-{[2-(methylamino)pyrimidin-5-yl]ethynyl}phenyl)urea

N-(5-*tert*-butylisoxazol-3-yl)-*N'*-{3-[(2-chloropyrimidin-5-yl)ethynyl]phenyl}urea (Intermediate 9) (94 mg) was stirred in methylamine (33% wt. solution in ethanol) (5 mL) and hydrogen chloride (1.0M solution in diethyl ether) (0.25 mL) was added dropwise. The reaction mixture was stirred at 80°C for 3 hours. The solvent was evaporated and the residue was purified by trituration with diethyl ether (20 mL) to give the title compound as a white solid (50 mg, 54%);

^{1}H NMR (DMSO-d_6) 1.30 (s, 9H), 2.84 (d, 3H), 6.49 (s, 1H), 7.10-7.16 (m, 1H), 7.30-7.36 (m, 2H), 7.57 (q, 1H), 7.72 (s, 1H), 8.42-8.53 (m, 2H), 8.89 (s, 1H), 9.48 (bs, 1H);

MS m/e MH^+ 391.

Intermediate 8

{3-[(2-chloropyrimidin-5-yl)ethynyl]phenyl}amine

Palladium (10 wt.%) on activated carbon (1.5 g) was added to a stirred solution of 5-bromo-2-chloropyrimidine (12.76 g) and 3-ethynyl aniline (9.28 g) in DIPEA (120 mL) under an inert atmosphere. The reaction mixture was stirred at 80°C for 4 hours. The reaction mixture was filtered through diatomaceous earth and washed with DCM. The filtrate was purified by flash chromatography on silica using 0-30% EtOAc in DCM as eluent. The resultant solid was triturated with ether to give the title compound as a cream solid (4.28 g, 28%);

^{1}H NMR (DMSO-d_6) 5.31 (s, 2H), 6.64 (dd, 1H), 6.69-6.76 (m, 2H), 7.08 (dd, 1H), 8.94 (s, 2H);

MS m/e $(MH+ MeCN)^+$ 271.

Intermediate 9

***N*-(5-*tert*-butylisoxazol-3-yl)-*N*'-{3-[(2-chloropyrimidin-5-yl)ethynyl]phenyl}urea**

Phenyl (5-tert-butylisoxazol-3-yl)carbamate (Intermediate 4) (526 mg) was added to a stirred solution of {3-[(2-chloropyrimidin-5-yl)ethynyl]phenyl}amine (Intermediate 8) (387 mg) and triethylamine (0.28 mL) in THF (10 mL). The reaction mixture was heated at 75°C for 4 hours. The solvent was evaporated and the residue was purified by trituration with ether (20 mL) to give the title compound as a white solid (520 mg, 78%);

^{1}H NMR (DMSO-d_6) 1.28 (s, 9H), 6.49 (s, 1H), 7.23-7.27 (m, 1H), 7.36-7.41 (m, 2H), 7.88 (s, 1H), 8.96 (s, 1H), 9.00 (s, 2H), 9.58 (s, 1H);

MS m/e MH^+ 396.

Examples 26 to 31 were prepared by an analogous method to Example 25 (using the appropriate starting materials).

Example 26

N-(5-tert-butylisoxazol-3-yl)-N'-(3-{[2-(dimethylamino)pyrimidin-5-yl]ethynyl}phenyl)urea

Starting Materials: Intermediate 9 and dimethylamine.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 3.15 (s, 6H), 6.49 (s, 1H), 7.12-7.16 (m, 1H), 7.30-7.34 (m, 2H), 7.74 (s, 1H), 8.52 (s, 2H), 8.88 (s, 1H), 9.54 (s, 1H);

MS m/e MH^+ 405.

Example 27

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 4-(2-aminoethyl)morpholine.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 2.37-2.41 (m, 4H), 2.44-2.51 (m, 2H + DMSO), 3.39-3.46 (m, 2H), 3.53-3.58 (m, 4H), 6.48 (s, 1H), 7.11-7.16 (m, 1H), 7.30-7.34 (m, 2H), 7.50 (t, 1H), 7.72 (s, 1H), 8.48 (s, 2H), 8.89 (s, 1H);

MS m/e MH^+ 490.

Example 28

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 4-(3-aminopropyl)morpholine.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 1.69 (m, 2H), 2.29-2.35 (m, 6H), 3.28-3.37 (m, 2H), 3.54-3.57 (m, 4H), 6.48 (s, 1H), 7.11-7.15 (m, 1H), 7.30-7.34 (m, 2H), 7.69 (t, 1H), 7.73 (s, 1H), 8.46 (bs, 2H), 8.88 (s, 1H);

MS m/e MH^+ 504.

Example 29

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-methoxyethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 2-methoxyethylamine.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 3.24 (s, 3H), 3.45-3.49 (m, 4H), 6.49 (s, 1H), 7.12-7.16 (m, 1H), 7.31-7.35 (m, 2H), 7.61-7.66 (m, 1H), 7.73 (s, 1H), 8.47 (s, 2H), 8.88 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 435.

Example 30

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[3-(1H-imidazol-1-yl)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

Starting Materials: Intermediate 9 and 1-(3-aminopropyl)imidazole.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 1.96 (qt, 2H), 3.21-3.32 (m, 2H + H_2O), 4.02 (t, 2H), 6.48 (s, 1H), 6.88 (s, 1H), 7.12-7.16 (m, 1H), 7.19 (s, 1H), 7.30-7.33 (m, 2H), 7.62 (s, 1H), 7.73 (s, 1H), 7.77 (t, 1H), 8.48 (s, 2H), 8.92 (s, 1H);

MS m/e MH^+ 485.

Example 31

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(3-methoxypropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 3-methoxypropylamine.

^1H NMR (DMSO-d_6) 1.29 (s, 9H), 1.75 (m, 2H), 3.21 (s, 3H), 3.30-3.39 (m, 4H), 6.49 (s, 1H), 7.12-7.16 (m, 1H), 7.30-7.33 (m, 2H), 7.66 (t, 1H), 7.72 (s, 1H), 8.47 (s, 2H), 8.94 (s, 1H);

MS m/e M-H^+ 447.

Examples 32 to 46 were prepared by an analogous method to Example 25 (using the appropriate starting materials). Purification was by flash chromatography on silica using 1-12% MeOH/NH_3 in DCM as eluent. The resultant solid was then triturated with ether.

Example 32

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-hydroxyethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 2-aminoethanol.

^1H NMR (DMSO-d_6) 1.29 (s, 9H), 3.32-3.40 (m, 2H), 3.48-3.56 (m, 2H), 4.67 (t, 1H), 6.49 (s, 1H), 7.12-7.16 (m, 1H), 7.30-7.32 (m, 2H), 7.54 (t, 1H), 7.72 (s, 1H), 8.45 (bs, 2H), 8.88 (s, 1H), 9.54 (s, 1H);

MS m/e MH^+ 421.

Example 33

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 1-(2-aminoethyl)pyrrolidine.

^1H NMR (DMSO-d_6) 1.29 (s, 9H), 1.63-1.72 (m, 4H), 2.42-2.55 (m, 4H+DMSO), 2.55-2.62 (m, 2H), 3.37-3.46 (m, 2H), 6.49 (s, 1H), 7.12-7.17 (m, 1H), 7.28-7.35 (m, 2H), 7.51 (t, 1H), 7.72 (s, 1H), 8.46 (s, 2H), 8.89 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 474.

Example 34

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 1-(3-aminopropyl)pyrrolidine.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 1.64-1.75 (m, 6H), 2.36-2.46 (m, 6H), 3.27-3.37 (m, 2H), 6.49 (s, 1H), 7.11-7.16 (m, 1H), 7.30-7.34 (m, 2H), 7.65-7.74 (m, 2H), 8.46 (s, 2H), 8.88 (s, 1H), 9.54 (s, 1H);

MS m/e MH^+ 488.

Example 35

N-[3-({2-[(2-aminoethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]-N'-(5-tert-butylisoxazol-3-yl)urea

Starting Materials: Intermediate 9 and ethylenediamine.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 2.68 (t, 2H), 3.24-3.36 (m, 2H+ H_2O), 6.49 (s, 1H), 7.11-7.16 (m, 1H), 7.31-7.35 (m, 2H), 7.61 (t, 1H), 7.73 (s, 1H), 8.46 (s, 2H), 8.92 (s, 1H);

MS m/e MH^+ 420.

Example 36

N-[3-({2-[(3-aminopropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]-N'-(5-tert-butylisoxazol-3-yl)urea

Starting Materials: Intermediate 9 and 1-(3-diaminopropane).

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 1.60 (m, 2H), 2.60 (t, 2H), 3.22-3.39 (m, 2H+ H_2O), 6.49 (s, 1H), 7.10-7.15 (m, 1H), 7.29-7.36 (m, 2H), 7.66-7.74 (m, 2H), 8.62 (s, 2H), 8.99 (s, 1H);

MS m/e MH^+ 434.

Example 37

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[2-(dimethylamino)ethyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

Starting Materials: Intermediate 9 and 1-(2-dimethylaminoethylamine).

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 2.16 (s, 6H), 2.40 (t, 2H), 3.39 (dd, 2H), 6.49 (s, 1H), 7.12-7.16 (m, 1H), 7.31-7.34 (m, 2H), 7.46 (t, 1H), 7.72 (s, 1H), 8.46 (s, 2H), 8.88 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 448.

Example 38

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[3-(dimethylamino)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

Starting Materials: Intermediate 9 and 1-(3-dimethylaminopropylamine).

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 1.65 (m, 2H), 2.11 (s, 6H), 2.24 (t, 2H), 3.25-3.35 (m, 2H+ H_2O), 6.49 (s, 1H), 7.10-7.16 (m, 1H), 7.30-7.34 (m, 2H), 7.68 (t, 1H), 7.72 (s, 1H), 8.45 (s, 2H), 8.89 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 462.

Example 39

N-2-(5-{[3-({[(5-tert-butylisoxazol-3-yl)amino]carbonyl}amino)phenyl]ethynyl}pyrimidin-2-yl)glycinamide

Starting Materials: Intermediate 9 and glycinamide.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 3.85 (d, 2H), 6.49 (s, 1H), 6.96 (bs, 1H), 7.12-7.17 (m, 1H), 7.30-7.36 (m, 3H), 7.64 (t, 1H), 7.73 (s, 1H), 8.49 (s, 2H), 8.89 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 456.

Example 40

N-3-(5-{[3-({[(5-tert-butylisoxazol-3-yl)amino]carbonyl}amino)phenyl]ethynyl}pyrimidin-2-yl)-beta-alaninamide

Starting Materials: Intermediate 9 and beta-alaninamide.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 2.35 (t, 2H), 3.49 (dd, 2H), 6.49 (s, 1H), 6.79 (bs, 1H), 7.12-7.16 (m, 1H), 7.31-7.34 (m, 3H), 7.59 (t, 1H), 7.73 (s, 1H), 8.47 (s, 2H), 8.88 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 448.

Example 41

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[2-(1H-imidazol-4-yl)ethyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

Starting Materials: Intermediate 9 and histamine.

^{1}H NMR (DMSO-d_6) 1.29 (s, 9H), 2.76 (t, 2H), 3.52 (dd, 2H), 6.49 (s, 1H), 6.80 (s, 1H), 7.14 (t, 1H), 7.30-7.34 (m, 2H), 7.51 (s, 1H), 7.70-7.74 (m, 2H), 8.47 (s, 2H), 8.88 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 471.

Example 42

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-pyridin-2-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 2-(2-aminoethyl)pyridine.

^1H NMR (DMSO-d_6) 1.29 (s, 9H), 3.00 (t, 2H), 3.66 (dd, 2H), 6.50 (s, 1H), 7.11-7.29 (m, 3H), 7.30-7.34 (m, 2H), 7.65-7.76 (m, 3H), 8.44-8.51 (m, 3H), 8.88 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 482.

Example 43

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[3-(isopropylamino)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

Starting Materials: Intermediate 9 and N-isopropyl-1,3-propanediamine.

^1H NMR (DMSO-d_6) 0.95 (d, 6H), 1.29 (s, 9H), 1.63 (m, 2H), 2.46-2.56 (m, 2H+DMSO), 2.66 (m, 1H), 3.26-3.38 (m, 2H+H_2O), 6.49 (s, 1H), 7.10-7.16 (m, 1H), 7.30-7.34 (m, 2H), 7.70-7.74 (m, 2H), 8.45 (s, 2H), 8.89 (s, 1H);

MS m/e MH^+ 476.

Example 44

N-(5-tert-butylisoxazol-3-yl)-N'-{3-[(2-{[3-(4-methylpiperazin-1-yl)propyl]amino}pyrimidin-5-yl)ethynyl]phenyl}urea

Starting Materials: Intermediate 9 and 1-(3-aminopropyl)–4-methylpiperazine.

^1H NMR (DMSO-d_6) 1.29 (s, 9H), 1.66 (m, 2H), 2.13 (s, 3H), 2.34-2.36 (m, 10H), 3.26-3.35 (m, 2H+H_2O), 6.49 (s, 1H), 7.11-7.16 (m, 1H), 7.30-7.34 (m, 2H), 7.67 (t, 1H), 7.72 (s, 1H), 8.45 (s, 2H), 8.88 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 517.

Example 45

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(2-pyridin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 4-(2-aminoethyl)pyridine.

^1H NMR (DMSO-d_6) 1.29 (s, 9H), 2.87 (t, 2H), 3.58 (q, 2H), 6.49 (s, 1H), 7.11-7.16 (m, 1H),

7.22-7.27 (m, 2H), 7.30-7.34 (m, 2H), 7.72 (s, 1H), 7.76 (t, 1H), 8.42-8.49 (m, 4H), 8.88 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 482.

Example 46

N-(5-tert-butylisoxazol-3-yl)-N'-[3-({2-[(3-piperidin-1-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 9 and 1-(3-aminopropyl)piperidine.

^1H NMR (DMSO-d_6) 1.29 (s, 9H), 1.33-1.47 (m, 2H), 1.44-1.53 (m, 4H), 1.67 (m, 2H), 2.27-2.37 (m, 6H), 3.24-3.35 (m, 2H+H_2O), 6.49 (s, 1H), 7.10-7.16 (m, 1H), 7.27-7.35 (m, 2H), 7.68-7.74 (m, 2H), 8.45 (s, 2H), 8.93 (s, 1H), 9.58 (s, 1H);

MS m/e MH^+ 502.

Example 47

N-(5-methylisoxazol-3-yl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Phenyl (3-methylisoxazol-5-yl)carbamate (Intermediate 3) (102 mg) was added to a stirred solution of 5-[(3-aminophenyl)ethynyl]-*N*-(2-pyrrolidin-1-ylethyl)pyrimidin-2-amine (Intermediate 10) (120 mg) and triethylamine (0.065 mL) in THF (10 mL). The reaction mixture was heated at 80°C for 3 hours. The solvent was evaporated and the product was purified by flash chromatography on silica using 0-10% MeOH/NH_3 in DCM as eluent. The resultant solid was triturated with ether to give the title compound as a white solid (121 mg, 72%);

^1H NMR (DMSO-d_6) 1.63-1.70 (m, 4H), 2.16 (s, 3H), 2.44-2.52 (m, 4H+DMSO), 2.57 (t, 2H), 3.37-3.45 (m, 2H), 5.95 (s, 1H), 7.13-7.17 (m, 1H), 7.29-7.39 (m, 2H), 7.53 (t, 1H), 7.69 (s, 1H), 8.46 (s, 2H), 8.93 (s, 1H), 10.12 (s, 1H);

MS m/e MH^+ 432.

Intermediate 10

AZ12273115

5-[(3-aminophenyl)ethynyl]-*N*-(2-pyrrolidin-1-ylethyl)pyrimidin-2-amine

{3-[(2-chloropyrimidin-5-yl)ethynyl]phenyl}amine (Intermediate 8) (726 mg) and 1-(2-aminoethyl)-pyrrolidine (3.6 g) were stirred in acetonitrile (10 mL) and hydrogen chloride

(1.0M solution in diethyl ether) (3.80 mL) was added dropwise. The reaction mixture was stirred and heated at 80°C for 3 hours. The solvent was evaporated and the product was purified by flash chromatography on silica using 0-10% MeOH/NH_3 in DCM as eluent to give the title compound as an off white solid (738 mg, 76%);

^{1}H NMR (DMSO-d_6) 1.63-1.69 (m, 4H), 2.42-2.52 (m, 4H+DMSO), 2.56 (m, 2H), 3.40 (m, 2H), 5.19 (s, 2H), 6.53 (dd, 1H), 6.61 (d, 1H), 6.67 (s, 1H), 7.01 (t, 1H), 7.46 (t, 1H), 8.41 (s, 2H);

MS m/e MH^+ 308.

Intermediates 11 and 12 were prepared by an analogous method to Intermediate 10 by using Intermediate 8 and the appropriate amine.

Intermediate 11

5-[(3-aminophenyl)ethynyl]-*N*-(2-morpholin-4-ylethyl)pyrimidin-2-amine

Starting Materials: Intermediate 8 and 1-(2-aminoethyl)morpholine.

^{1}H NMR (DMSO-d_6) 2.36-2.52 (m, 6H+DMSO), 3.41 (m, 2H), 3.55 (m, 4H), 5.19 (s, 2H), 6.54-6.57 (m, 1H), 6.61 (d, 1H), 6.67 (s, 1H), 7.01 (t, 1H), 7.43 (t, 1H), 8.41 (s, 2H);

MS m/e MH^+ 324.

Intermediate 12

5-[(3-aminophenyl)ethynyl]-*N*-(3-morpholin-4-ylpropyl)pyrimidin-2-amine

Starting Materials: Intermediate 8 and 1-(3-aminopropyl)morpholine.

^{1}H NMR (DMSO-d_6) 1.67 (m, 2H), 2.28-2.36 (m, 6H), 3.27-3.35 (m, 2H+H_2O), 3.53-3.58 (m, 4H), 5.19 (s, 2H), 6.54-6.58 (m, 1H), 6.60 (d, 1H), 6.66 (s, 1H), 7.01 (t, 1H), 7.62 (t, 1H), 8.66 (s, 2H);

MS m/e MH^+ 338.

Examples 48 and 49 were prepared by an analogous method to Example 47, using Intermediate 10 with the appropriate phenyl carbamate.

Example 48

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and Intermediate 2.

^{1}H NMR (DMSO-d_6) 1.38 (s, 9H), 1.65-1.73 (m, 4H), 2.46-2.58 (m, 4H+DMSO), 2.64 (t, 2H), 3.43 (m, 2H), 7.13 (d, 1H), 7.32 (t, 1H), 7.49-7.57 (t, 2H), 7.82 (s, 1H), 8.47 (s, 2H), 9.66 (bs, 1H), 11.40 (bs, 1H);

MS m/e MH^+ 491.

Example 49

N-(3-methylisothiazol-5-yl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and Intermediate 7.

^{1}H NMR (DMSO-d_6) 1.63-1.70 (m, 4H), 2.28 (s, 3H), 2.44-2.52 (m, 4H+DMSO), 2.58 (t, 2H), 3.42 (m, 2H), 6.66 (s, 1H), 7.13-7.18 (m, 1H), 7.29-7.41 (m, 2H), 7.53 (t, 1H), 7.72 (s, 1H), 8.47 (s, 2H), 9.20 (s, 1H), 10.39 (s, 1H);

MS m/e MH^+ 448.

Examples 50 to 56 were prepared by an analogous method to Example 1 by using Intermediate 10 with the appropriate isocyanate.

Example 50

N-(3-fluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and 3-fluorophenylisocyanate.

^{1}H NMR (DMSO-d_6) 1.63-1.70 (m, 4H), 2.43-2.52 (m, 4H+DMSO), 2.57 (t, 2H), 3.37-3.46 (m, 2H), 6.74-6.82 (m, 1H), 7.11 (d, 2H), 7.25-7.36 (m, 3H), 7.44-7.55 (m, 2H), 7.72 (s, 1H), 8.46 (s, 2H), 8.83 (s, 1H), 8.94 (s, 1H);

MS m/e MH^+ 445.

Example 51

N-(4-methoxyphenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and 4-methoxyphenylisocyanate.

^{1}H NMR (DMSO-d_6) 1.63-1.69 (m, 4H), 2.42-2.52 (m, 4H+DMSO), 2.57 (t, 2H), 3.41 (m, 2H), 3.71 (s, 3H), 6.83-6.89 (m, 2H), 7.04-7.10 (m, 1H), 7.24-7.38 (m, 4H), 7.51 (t, 1H), 7.71 (s, 1H), 8.43-8.51 (m, 3H), 8.67 (s, 1H);

MS m/e MH^+ 457.

Example 52

N-(2-fluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and 2-fluorophenylisocyanate.

^{1}H NMR (DMSO-d_6) 1.61-1.71 (m, 4H), 2.43-2.52 (m, 4H+DMSO), 2.57 (t, 2H), 3.38-3.46 (m, 2H), 6.96-7.05 (m, 1H), 7.09-7.32 (m, 5H), 7.51 (t, 1H), 7.74 (s, 1H), 8.11 (m, 1H), 8.47 (s, 2H), 8.56 (s, 1H), 9.13 (s, 1H);

MS m/e MH^+ 445.

Example 53

N-(2,5-difluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and 2,5-difluorophenylisocyanate.

^{1}H NMR (DMSO-d_6) 1.63-1.70 (m, 4H), 2.44-2.52 (m, 4H+DMSO), 2.57 (t, 2H), 3.41 (m, 2H), 6.78-6.86 (m, 1H), 7.11-7.16 (m, 1H), 7.24-7.34 (m, 3H), 7.52 (t, 1H), 7.74 (s, 1H), 8.02 (m, 1H), 8.47 (s, 2H), 8.78 (s, 1H), 9.22 (s, 1H);

MS m/e MH^+ 463.

Example 54

N-(3,4-difluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and 3,4-difluorophenylisocyanate.

^{1}H NMR (DMSO-d_6) 1.63-1.71 (m, 4H), 2.42-2.53 (m, 4H+DMSO), 2.57 (t, 2H), 3.40 (m, 2H), 7.09-7.16 (m, 2H), 7.27-7.37 (m, 3H), 7.51 (t, 1H), 7.60-7.72 (m, 2H), 8.47 (s, 2H), 8.83 (s,

1H), 8.93 (s, 1H);
MS m/e MH^+ 463.

Example 55

N-[2-fluoro-5-(trifluoromethyl)phenyl]-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and 2-fluoro-5-trifluoromethylphenylisocyanate.
^1H NMR (DMSO-d_6) 1.63-1.71 (m, 4H), 2.45-2.52 (m, 4H+DMSO), 2.58 (t, 2H), 3.37-3.45 (m, 2H), 7.12-7.16 (m, 1H), 7.26-7.56 (m, 5H), 7.77 (s, 1H), 8.47 (s, 2H), 8.59 (dd, 1H), 8.92 (s, 1H), 9.27 (s, 1H);
MS m/e MH^+ 513.

Example 56

N-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]-N'-[4-(trifluoromethyl)phenyl]urea

Starting Materials: Intermediate 10 and 4-trifluoromethylphenylisocyanate.
^1H NMR (DMSO-d_6) 1.64-1.72 (m, 4H), 2.41-2.53 (m, 4H+DMSO), 2.57 (t, 2H), 3.41 (m, 2H), 7.12 (d, 1H), 7.29-7.39 (m, 2H), 7.52 (t, 1H), 7.60-7.68 (m, 4H), 7.72 (s, 1H), 8.46 (s, 2H), 8.88 (s, 1H), 9.12 (s, 1H);
MS m/e MH^+ 495.

Examples 57 to 59 were prepared by an analogous method to Example 1 using Intermediate 10 with the appropriate isocyanate, except purification was by trituration with hot methanol.

Example 57

N-1,3-benzodioxol-5-yl-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and (3,4-methylenedioxy)phenyl isocyanate.
^1H NMR (DMSO-d_6) 1.62-1.71 (m, 4H), 2.42-2.53 (m, 4H+DMSO), 2.57 (t, 2H), 3.41 (m, 2H), 5.96 (s, 2H), 6.72-6.84 (m, 2H), 7.05-7.11 (m, 1H), 7.17-7.20 (m, 1H), 7.25-7.34 (m, 2H), 7.51 (t, 1H), 7.70 (s, 1H), 8.42-8.49 (s, 2H), 8.58 (s, 1H), 8.69 (s, 1H);
MS m/e MH^+ 471.

Example 58

N-(4-fluorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and 4-fluorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 1.62-1.70 (m, 4H), 2.42-2.52 (m, 4H+DMSO), 2.57 (t, 2H), 3.41 (m, 2H), 7.06-7.16 (m, 3H), 7.26-7.36 (m, 2H), 7.40-7.55 (m, 3H), 7.71 (s, 1H), 8.46 (s, 2H), 8.71-8.77 (m, 2H);

MS m/e MH^+ 445.

Example 59

N-(3-chlorophenyl)-N'-[3-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 10 and 3-chlorophenyl isocyanate.

^{1}H NMR (DMSO-d_6) 1.63-1.70 (m, 4H), 2.43-2.52 (m, 4H+DMSO), 2.57 (t, 2H), 3.41 (m, 2H), 7.02 (dt, 1H), 7.11 (d, 1H), 7.22-7.37 (m, 4H), 7.52 (t, 1H), 7.69-7.74 (m, 2H), 8.46 (s, 2H), 8.85 (s, 1H), 8.92 (s, 1H);

MS m/e MH^+ 461.

Example 60

N-(5-methylisoxazol-3-yl)-N'-[3-({2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Example 60 was prepared by an analogous method to Example 47 using Intermediate 11 and Intermediate 3.

^{1}H NMR (DMSO-d_6) 2.16 (s, 3H), 2.36-2.52 (m, 6H+DMSO), 3.43 (m, 2H), 3.52-3.58 (m, 4H), 5.95 (s, 1H), 7.12-7.18 (m, 1H), 7.29-7.38 (m, 2H), 7.49 (t, 1H), 7.70 (s, 1H), 8.46 (s, 2H), 8.92 (s, 1H), 10.12 (s, 1H);

MS m/e MH^+ 448.

Example 61

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[3-({2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Example 61 was prepared by an analogous method to Example 47, using Intermediate 11 and Intermediate 2.. Purification was by trituration with methanol.

^{1}H NMR (DMSO-d_6) 1.38 (s, 9H), 2.36-2.52 (m, 6H+DMSO), 3.43 (m, 2H), 3.53-3.58 (m, 4H), 7.15 (d, 1H), 7.33 (t, 1H), 7.39-7.45 (m, 1H), 7.49 (t, 1H), 7.76 (s, 1H), 8.47 (s, 2H), 9.16 (s, 1H);

MS m/e MH^+ 507.

Example 62

N-[2-fluoro-5-(trifluoromethyl)phenyl]-N'-[3-({2-[(2-morpholin-4-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Example 62 was prepared by an analogous method to Example 1, using Intermediate 11 and 2-fluoro-5-trifluoromethylphenyl isocyanate.

^{1}H NMR (DMSO-d_6) 2.36-2.52 (m, 6H+DMSO), 3.43 (m, 2H), 3.52-3.58 (m, 4H), 7.14 (d, 1H), 7.26-7.34 (m, 2H), 7.35-7.42 (m, 1H), 7.45-7.53 (m, 2H), 7.78 (s, 1H), 8.47 (s, 2H), 8.59 (dd, 1H), 8.91 (s, 1H), 9.25 (s, 1H);

MS m/e MH^+ 529.

Examples 63 and 64 were prepared by an analogous method to Example 47 except using Intermediate 12 in place of Intermediate 10 with the appropriate phenylcarbamate.

Example 63

N-(5-methylisoxazol-3-yl)-N'-[3-({2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 12 and Intermediate 3.

^{1}H NMR (DMSO-d_6) 1.68 (m, 2H), 2.16 (s, 3H), 2.29-2.37 (m, 6H), 3.26-3.37 (m, 2H+H_2O), 3.53-3.58 (m, 4H), 5.95 (s, 1H), 7.13-7.17 (m, 1H), 7.29-7.38 (m, 2H), 7.66-7.72 (m, 2H), 8.46 (s, 2H), 8.93 (s, 1H), 10.12 (s, 1H);

MS m/e MH^+ 462.

Example 64

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[3-({2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Starting Materials: Intermediate 12 and Intermediate 2.

^{1}H NMR (DMSO-d_6) 1.38 (s, 9H), 1.68 (m, 2H), 2.29-2.39 (m, 6H), 3.26-3.37 (m, 2H+H_2O), 3.53-3.58 (m, 4H), 7.15 (d, 1H), 7.33 (t, 1H), 7.40-7.45 (m, 1H), 7.68 (t, 1H), 7.76 (s, 1H), 8.46 (s, 2H), 9.21 (s, 1H);

MS m/e MH^+ 521.

Example 65

N-[2-fluoro-5-(trifluoromethyl)phenyl]-N'-[3-({2-[(3-morpholin-4-ylpropyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Example 65 was prepared by an analogous method to Example 1 using Intermediate 12 and 2-fluoro-5-trifluoromethylphenyl isocyanate.

^{1}H NMR (DMSO-d_6) 1.68 (m, 2H), 2.29-2.37 (m, 6H), 3.25-3.37 (m, 2H+H_2O), 3.53-3.58 (m, 4H), 7.14 (dt, 1H), 7.26-7.34 (m, 2H), 7.35-7.42 (m, 1H), 7.45-7.53 (m, 1H), 7.68 (t, 1H), 7.78 (s, 1H), 8.47 (s, 2H), 8.59 (dd, 1H), 8.91 (d, 1H), 9.25 (s, 1H);

MS m/e MH^+ 543.

Example 66

N-(5-methylisoxazol-3-yl)-N'-[4-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Example 66 was prepared by an analogous method to Example 47 using Intermediate 14 and Intermediate 3.

^{1}H NMR (DMSO-d_6) 1.66-1.70 (m, 4H), 2.18 (s, 3H), 2.46-2.52 (m, 4H+DMSO), 2.59 (t, 2H), 3.37-3.45 (m, 2H), 5.97 (s, 1H), 7.43-7.53 (m, 5H), 8.44 (s, 2H), 9.02 (s, 1H), 10.11 (s, 1H);

MS m/e MH^+ 432.

Intermediate 13

{4-[(2-chloropyrimidin-5-yl)ethynyl]phenyl}amine

Intermediate 13 was prepared by an analogous method to Intermediate 8, except using 4-ethynylaniline in place of 3-ethynylaniline.

^{1}H NMR (DMSO-d_6) 5.72 (s, 2H), 6.57 (d, 2H), 7.23 (d, 2H), 8.85 (s, 2H);

MS m/e $(M+CH_3CN)^+$ 271.

Intermediate 14

5-[(4-aminophenyl)ethynyl]-*N*-(2-pyrrolidin-1-ylethyl)pyrimidin-2-amine

Intermediate 14 was prepared by an analogous method to Intermediate 10, by using Intermediate 13 in place of Intermediate 8.

^{1}H NMR (DMSO-d_6) 1.62-1.69 (m, 4H), 2.42-2.51 (m, 4H+DMSO), 2.56 (m, 2H), 3.39 (m, 2H), 5.49 (s, 2H), 6.52 (d, 2H), 7.14 (d, 2H), 7.35 (t, 1H), 8.35 (s, 2H);

MS m/e MH^+ 308.

Example 67

N-(5-tert-butylisoxazol-3-yl)-N'-[4-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Example 67 was prepared by an analogous method to Example 47 but using Intermediate 14 and Intermediate 4.

^{1}H NMR (DMSO-d_6) 1.30 (s, 9H), 1.65-1.71 (m, 4H), 2.44-2.53 (m, 4H+DMSO), 2.59 (m, 2H), 3.42 (m, 2H), 6.51 (s, 1H), 7.42-7.52 (m, 5H), 8.44 (s, 2H), 8.98 (s, 1H), 9.55 (s, 1H);

MS m/e MH^+ 474.

Example 68

N-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-N'-[4-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Example 68 was prepared by an analogous method to Example 47 but using Intermediate 14 and Intermediate 2. Purification was by trituration with ether and methanol.

^{1}H NMR (DMSO-d_6) 1.40 (s, 9H), 1.67-1.72 (m, 4H), 2.48-2.56 (m, 4H+DMSO), 2.63 (t, 2H), 3.40-3.47 (m, 2H), 7.45 (d, 2H), 7.49 (t, 1H), 7.61 (d, 2H), 8.45 (s, 2H), 9.55 (bs, 1H), 11.45 (bs, 1H);

MS m/e MH^+ 491.

Example 69

N-[2-fluoro-5-(trifluoromethyl)phenyl]-N'-[4-({2-[(2-pyrrolidin-1-ylethyl)amino]pyrimidin-5-yl}ethynyl)phenyl]urea

Example 69 was prepared by an analogous method to Example 1 but using Intermediate and 2-fluoro-5-trifluoromethylphenyl isocyanate.

^{1}H NMR (DMSO-d_6) 1.63-1.70 (m, 4H), 2.45-2.51 (m, 4H+DMSO), 2.56 (t, 2H), 3.36-3.45 (m, 2H), 7.36-7.53 (m, 7H), 8.43 (s, 2H), 8.59 (dd, 1H), 8.93 (s, 1H), 9.34 (s, 1H);
MS m/e MH^+ 513.

Example 70

N-(5-{[3-({[(5-tert-butylisoxazol-3-yl)amino]carbonyl}amino)phenyl]ethynyl}pyrimidin-2-yl)-2-(2-methoxyethoxy)acetamide

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(5-tert-butylisoxazol-3-yl)urea (Example 22) (100 mg) and 2-(2-methoxyethoxy)acetic acid (71 mg) were stirred in pyridine (8 mL) and phosphorous oxychloride (0.050 mL) was added dropwise. The reaction mixture was stirred at 25 °C for 1 hour. The solvent was evaporated and the residue was purified by reverse phase HPLC using 0-100% MeCN in water (0.2% TFA) as eluent to give the title compound as an off-white solid. (15 mg, 12%);
^{1}H NMR ($CDCl_3$) 1.29 (s, 9H), 3.41 (s, 3H), 3.54-3.59 (m, 2H), 3.71-3.76 (m, 2H), 4.16 (s, 2H), 5.84 (s, 1H), 7.18-7.29 (m, 2H), 7.46-7.51 (m, 1H), 7.71 (s, 1H), 7.82 (bs, 1H), 8.67 (s, 2H), 9.28 (bs, 1H), 9.59 (s, 1H);
MS m/e MH^+ 493.

Example 71

N-{6-[(2-aminopyrimidin-5-yl)ethynyl]pyridin-2-yl}-N'-(5-tert-butylisoxazol-3-yl)urea

$PdCl_2$dppf (37 mg) was added to a degassed solution of *N*-(5-*tert*-butylisoxazol-3-yl)-*N'*-(6-iodopyridin-2-yl)urea (Intermediate 16) (550 mg), 5-ethynylpyrimidin-2-amine (Intermediate 18) (119 mg), CuI (4 mg) and Et_3N (5 mL) in DMF (20 mL). The reaction was stirred at ambient temperature under an inert atmosphere for 24 hours. The solvent was evaporated *in vacuo* and the residue diluted with DCM (30 mL) and water (20 mL). The organic phase was separated and then washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica using 0-10% MeOH in DCM as the eluent followed by reverse phase HPLC, gradient H_2O:MeCN (0-70%) gave the title compound as a beige solid (28 mg, 7%);
^{1}H NMR (DMSO-d_6) 1.33 (s, 9H), 6.56 (s, 1H), 7.26 (s, 1H), 7.28 (s, 2H), 7.67 (d, 1H), 7.83 (t, 1H), 8.49 (s, 2H), 9.67 (s, 1H), 10.53 (s, 1H);
MS m/e MH^+ 378.

Intermediate 15

6-iodopyridin-2-amine

2-Bromo-6-aminopyridine (519 mg), CuI (29 mg), NaI (899 mg) and N,N-dimethylethylenediamine (26 mg) in dioxane (5 mL) were heated at 110 °C under an inert atmosphere for 6 hours. Concentrated NH_3 (8 mL) then water (10 mL) was added. The product was then extracted with DCM (3 x 15 mL), dried ($MgSO_4$), filtered and concentrated. The product was purified by flash chromatography on silica using 0-10% MeOH in DCM as the eluent to give the title compound as a beige solid (530 mg, 80%);

^{1}H NMR ($CDCl_3$) 4.60 (s, 2H), 6.41-6.44 (m, 1H), 7.00-7.08 (m, 2H);

MS m/e MH^+ 221.

Intermediate 16

***N*-(5-*tert*-butylisoxazol-3-yl)-*N'*-(6-iodopyridin-2-yl)urea**

Intermediate 16 was prepared by an analogous method to Example 24 using Intermediate 15 and Intermediate 2. Purification was by flash chromatography on silica using 0-10% methanol in dichloromethane as the eluent.

MS m/e MH^+ 378.

Intermediate 17

5-[(trimethylsilyl)ethynyl]pyrimidin-2-amine

$PdCl_2$dppf (146 mg) was added to a solution of 2-amino-5-iodopyrimidine (221 mg), trimethylsilylacetylene (491 mg), CuI (57 mg) and DIPEA (259 mg) in EtOAc (5 mL) at -20°C under an inert atmosphere. The reaction was allowed to warm to ambient temperature and stirred for 6 hours. The reaction mixture was diluted with water (10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated. The crude product was used directly without further purification (191 mg, 100%);

^{1}H NMR ($CDCl_3$); 0.26 (s, 9H), 5.19 (bs, 2H), 8.39 (s, 2H);

MS m/e MH^++MeCN 233.

Intermediate 18

5-ethynylpyrimidin-2-amine

K_2CO_3 (276 mg) was added to a solution of 5-[(trimethylsilyl)ethynyl]pyrimidin-2-amine (Intermediate 17) (191 mg) in MeOH (40 mL):water (20 mL). The reaction mixture was

allowed to stir at ambient temperature under an inert atmosphere for 24 hours then neutralised with HCl (1M). The reaction mixture was then concentrated and the resultant residue dissolved in DCM (30 mL). The DCM phase was washed with water (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was used directly without further purification (119 mg, 100%);

^{1}H NMR ($CDCl_3$); 3.19 (s, 1H), 5.26 (bs, 2H), 8.41 (s, 2H);

MS m/e MH^++MeCN 161.

Example 72

N-{2-[(2-aminopyrimidin-5-yl)ethynyl]pyridin-4-yl}-N'-(5-tert-butylisoxazol-3-yl)urea

Example 72 was prepared by an analogous method to Example 71 but using Intermediate 20 and Intermediate 18 and without RPHPLC purification.

^{1}H NMR (DMSO-d_6) 1.32 (s, 9H), 6.54 (s, 1H), 7.24 (s, 2H), 7.24-7.36 (m, 1H), 7.77 (s, 1H), 8.39-8.50 (m, 3H), 9.28 (s, 1H), 9.82 (s, 1H);

MS m/e MH^+ 378.

Intermediate 19

2-iodopyridin-4-amine

Intermediate 19 was prepared by an analogous method to Intermediate 15 but using 2-bromo-4-aminopyridine in place of 2-bromo-6-aminopyridine.

MS m/e MH^+ 221.

Intermediate 20

***N*-(5-*tert*-butylisoxazol-3-yl)-*N'*-(2-iodopyridin-4-yl)urea**

Intermediate 20 was prepared by an analogous method to Example 24 using Intermediate 2 and Intermediate 19. Purification was by flash chromatography on silica using 0-10% methanol in dichloromethane as the eluent.

MS m/e MH^+ 387.

Example 73

N-{5-[(2-aminopyrimidin-5-yl)ethynyl]-1,3-thiazol-2-yl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

A mixture of 2-amino-5-ethynylpyrimidine (Intermediate 18) (60 mg), *N*-(5-bromo-1,3-thiazol-2-yl)-*N'*-[2-fluoro-5-(trifluoromethyl)phenyl]urea (Intermediate 21) (192 mg), 1,1,3,3-tetramethylguanidine (69 mg), and copper (I) iodide (5 mg) in dry DMF (1.5 mL) was stirred and degassed with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (58 mg) was added and the mixture heated at 80°C for 2.5 hours. The mixture was cooled, stirred, and diluted with water (15 mL). The solid formed was filtered off and dried. Purification by flash chromatography on silica using 0-30% MeOH in DCM as eluent, then trituration with DCM gave the title compound as a solid (60 mg, 28%);

^{1}H NMR (DMSO-d_6) 7.16(s, 2H), 7.45-7.60 (m, 2H), 7.70 (s, 1H), 8.42 (s, 2H), 8.53 (m, 1H), 9.23 (bs, 1H), 11.15 (bs, 1H);

MS m/e MH^+ 423.

Intermediate 21

***N*-(5-bromo-1,3-thiazol-2-yl)-*N'*-[2-fluoro-5-(trifluoromethyl)phenyl]urea**

2-Fluoro-5-(trifluoromethyl)phenyl isocyanate (1.02 g) was added to a stirred solution of 2-amino-5-bromothiazole (0.90 g) in dry DCM (20 mL) at ambient temperature. After 17 hours the precipitate was filtered off, washed with DCM then isohexane, and dried to give the title compound (1.38 g, 71%);

^{1}H NMR (DMSO-d_6) 7.45-7.60 (m, 3H), 8.50 (m, 1H), 9.20 (bs, 1H), 11.05 (bs, 1H);

MS m/e MH^+ 384, 386 (1 x Br).

Example 74

N-{5-[(2-aminopyrimidin-5-yl)ethynyl]-1,3,4-thiadiazol-2-yl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea

Example 74 was prepared by an analogous method to Example 73 but using Intermediate 22 and Intermediate 18.

^{1}H NMR (DMSO-d_6) 7.36 (s, 2H), 7.50-7.60 (m, 2H), 8.48 (m, 1H), 8.53 (s, 2H), 9.30 (bs, 1H), 11.50 (bs, 1H);

MS m/e MH^+ 424.

Intermediate 22

***N*-(5-bromo-1,3,4-thiadiazol-2-yl)-*N'*-[2-fluoro-5-(trifluoromethyl)phenyl]urea**

2-Fluoro-5-(trifluoromethyl)phenyl isocyanate (1.02 g) was added to a stirred solution of 2-amino-5-bromo-1,3,4-thiadiazole {Eur.J.Med.Chem.Chim.Ther. (1975) 121} (0.90 g) in dry THF (50 mL) at 50°C. After 17 hours at ambient temperature the solvent was evaporated and the residue was triturated with 1:1 isohexane / DCM. The solid formed was filtered off, washed with isohexane, and dried to give the title compound (1.90 g, 98%);

^{1}H NMR (DMSO-d_6) 7.50-7.60 (m, 2H), 8.43 (m, 1H), 9.25 (bs, 1H), 11.50 (bs, 1H);

MS m/e MH^+ 385, 387 (1 x Br).

Example 75

***N*-{5-[(2-aminopyrimidin-5-yl)ethynyl]-1,3-thiazol-2-yl}-*N'*-(5-*tert*-butylisoxazol-3-yl)urea**

Example 75 was prepared by an analogous method to Example 73 but using Intermediate 23 and Intermediate 18.

^{1}H NMR (DMSO-d_6) 1.30 (s, 9H), 6.55 (s, 1H), 7.15 (s, 2H), 7.69 (s, 1H), 8.43 (s, 2H), 9.82 (bs, 1H), 10.80 (bs, 1H);

MS m/e $(M-H)^-$ 382.

Intermediate 23

***N*-(5-bromo-1,3-thiazol-2-yl)-*N'*-(5-*tert*-butylisoxazol-3-yl)urea**

Triethylamine (1.3 mL) was added to a stirred mixture of phenyl (5-*tert*-butylisoxazol-3-yl)carbamate (Intermediate 4) (702 mg) and 2-amino-5-bromothiazole (483 mg) in 1,4-dioxane (20 mL) and heated at 90°C for 1 hour. The solvent was evaporated and the residue was purified by flash chromatography on silica using 0–50% EtOAc in DCM as eluent to give the title compound as a solid (205 mg, 20%);

^{1}H NMR (DMSO-d_6) 1.30 (s, 9H), 6.52 (s, 1H), 7.51 (s, 1H), 9.77 (bs, 1H), 10.73 (bs, 1H);

MS m/e MH^+ 345, 347 (1 x Br).

Example 76

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(2-methoxyphenyl)acetamide

A solution of 2-methoxyphenylacetic acid (50 mg) in DMF (1 mL) was added to HATU (120 mg) and polymer supported DIPEA (Argonaut Technologies, 3.9 $mmolg^{-1}$, 300 mg). The

mixture was shaken for 5 min. A solution of 5-[(3-aminophenyl)ethynyl]pyrimidine-2-amine (Intermediate 1) (68 mg) in DMF (1 mL) was added and agitation continued overnight. The resin was removed by filtration, and the solvent was added dropwise to water (10 mL) with shaking. The resulting solid was sonicated in fresh water (10 mL), filtered and dried to give the title compound (32 mg, 30%);

^{1}H NMR (DMSO-d_6) 3.63 (s, 2H), 3.76 (s, 3H), 6.89 (t, 1H), 6.97 (d, 1H), 7.10 (s, 2H), 7.15 (d, 1H), 7.18-7.27 (m, 2H), 7.32 (t, 1H), 7.51 (d, 1H), 7.83 (s, 2H), 8.41 (s, 1H);

MS m/e MH^+ 359.

Examples 77 to 81 were prepared by an analogous method to Example 76 by using the appropriate acid.

Example 77

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-phenylacetamide

Starting Materials: Intermediate 1 and phenylacetic acid.

^{1}H NMR (DMSO-d_6) 3.67 (s, 2H), 7.12 (bs, 2H), 7.18-7.20 (m, 1H), 7.22-7.28 (m, 1H), 7.33-7.37 (m, 6H), 7.52-7.54 (m, 1H), 7.85-7.86 (m, 1H), 8.44 (s, 2H);

MS m/e MH^+ 329.

Example 78

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(3-methoxyphenyl)acetamide

Starting Materials: Intermediate 1 and 3-methoxyphenylacetic acid.

^{1}H NMR (DMSO-d_6) 3.61 (s, 2H), 3.74 (s, 3H), 6.81 (d, 1H), 6.91 (s, 2H), 7.11 (s, 2H), 7.12-7.27 (m, 2H), 7.33 (t, 1H), 7.50 (d, 1H), 7.83 (s, 1H), 8.41 (s, 2H), 10.22 (s, 1H);

MS m/e MH^+ 359.

Example 79

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-[3-(trifluoromethyl)phenyl]acetamide

Starting Materials: Intermediate 1 and 3-trifluoromethylphenylacetic acid.

^{1}H NMR (DMSO-d_6) 3.79 (s, 2H), 7.11 (s, 2H), 7.17 (d, 1H), 7.33 (t, 1H), 7.49 (d, 1H), 7.52-7.66 (m, 3H), 7.69 (s, 1H), 7.83 (s, 1H), 8.41 (s, 2H), 10.31 (s, 1H);

MS m/e MH^+ 397.

Example 80

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-[4-(trifluoromethyl)phenyl]acetamide

Starting Materials: Intermediate 1 and 4-trifluoromethylphenylacetic acid.

^{1}H NMR (DMSO-d_6) 3.77 (s, 2H), 7.11 (s, 2H), 7.17 (d, 1H), 7.33 (t, 1H), 7.49 (d, 1H), 7.55 (d, 2H), 7.69 (d, 2H), 7.82 (s, 1H), 8.41 (s, 2H), 10.32 (s, 1H);

MS m/e MH^+ 397.

Example 81

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(3-methylisoxazol-5-yl)acetamide

Starting Materials: Intermediate 1 and 3-methyl-5-isoxazoleacetic acid.

^{1}H NMR (DMSO-d_6) 2.20 (s, 3H), 3.89 (s, 2H), 6.27 (s, 1H), 7.11 (s, 2H), 7.19 (d, 1H), 7.35 (t, 1H), 7.48 (d, 1H), 7.81 (s, 1H), 8.42 (s, 2H), 10.36 (s, 1H);

MS m/e MH^+ 334.

Intermediate 24

5-[(4-Aminophenyl)ethynyl]pyrimidin-2-amine

A mixture of 2-amino-5-iodopyrimidine (1.10 g), 4-ethynylaniline (0.82 g), 1,1,3,3-tetramethylguanidine (0.81 g), and copper (I) iodide (9.5 mg) in dry DMF (3.0 mL) was stirred and degassed with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (115 mg) was added and the mixture heated at 60 °C for 2.5 hours. The solvent was evaporated and the residue was triturated with DCM. The solid formed was filtered off and washed with water then dissolved in 1:1 DCM / MeOH, filtered then evaporated. The solid obtained was triturated with ether and dried to give the title compound (0.67 g, 63%);

^{1}H NMR (DMSO-d_6) 5.50 (s, 2H), 6.55 (d, 2H), 6.95 (s, 2H), 7.15 (d, 2H), 8.35 (s, 2H);

MS m/e MH^+ 211.

Examples 82 to 84 were prepared by an analogous method to Example 76 but using Intermediate 24 in place of Intermediate 1 with the appropriate acid.

Example 82

N-{4-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(2-methoxyphenyl)acetamide

Starting Materials: Intermediate 24 and 2-methoxyphenylacetic acid.

^{1}H NMR (DMSO-d_6) 3.64 (s, 2H), 3.76 (s, 3H), 6.89 (t, 1H), 6.97 (d, 1H), 7.06 (2H), 7.18-7.28 (m, 2H), 7.42 (d, 2H), 7.63 (d, 2H), 8.38 (s, 2H), 10.19 (s, 1H);
MS m/e MH^+ 359.

Example 83

N-{4-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-2-(3-methylisoxazol-5-yl)acetamide

Starting Materials: Intermediate 24 and 3-methyl-5-isoxazoleacetic acid.
^{1}H NMR (DMSO-d_6) 2.20 (s, 3H), 3.90 (s, 2H), 6.26 (s, 1H), 7.07 (s, 2H), 7.44 (d, 2H), 7.63 (d, 2H), 8.39 (s, 2H), 10.42 (s, 1H);
MS m/e MH^+ 334.

Example 84

N-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N'-(2,2-dimethyltetrahydro-2H-pyran-4-yl)urea

Example 84 was prepared by an analogous method to Example 24 by using the compound prepared in Example 23 and 2,2-dimethyltetrahydro-2H-pyran-4-ylamine.
^{1}H NMR (DMSO-d_6) 1.11-1.31 (m, 2H), 1.14 (s, 3H), 1.17 (s, 3H), 1.72-1.79 (dd, 2H), 3.52-3.67 (m, 2H), 3.72-3.88 (m, 1H), 6.05-6.11 (d, 1H), 6.98-7.04 (m, 1H), 7.09 (s, 2H), 7.18-7.27 (m, 2H), 7.65 (s, 1H), 8.40 (s, 2H), 8.42 (s, 1H);
MS m/e MH^+ 366.

Example 85

N-{6-[(2-aminopyrimidin-5-yl)ethynyl]pyrimidin-4-yl}-N'-(5-tert-butylisoxazol-3-yl)urea

Example 85 was prepared by an analogous method to Example 71 by using Intermediate 26 and Intermediate 18 and without RPHPLC purification.
^{1}H NMR (DMSO-d_6) 1.33 (s, 9H), 6.58 (s, 1H), 7.39 (s, 2H), 7.87 (d, 1H), 8.56 (s, 2H), 8.81 (d, 1H), 9.90 (s, 1H), 10.34 (s, 1H);
MS m/e MH^+ 379.

Intermediate 25

6-iodopyrimidin-4-amine

6-Chloropyrimidin-4-ylamine (450 mg) was added in portions to HI (57% wt. aq., 20 mL) at 0 °C. The reaction mixture was stirred for 30 minutes at 0 °C and then at ambient temperature

for 18 hours. The reaction mixture was treated with $NaHCO_3$ (sat. aq.) until pH8 was achieved and then the product extracted with EtOAc (2 x 30 mL). The combined organics were washed with NaOH (2M, aq.), dried ($MgSO_4$), filtered and then concentrated. The crude product was used directly without further purification (500 mg, 65%);

^{1}H NMR ($CDCl_3$); 6.90 (s, 1H), 7.03 (s, 2H), 8.05 (s, 1H);

MS m/e MH^+ 221.

Intermediate 26

***N*-(5-*tert*-butylisoxazol-3-yl)-*N*'-(6-iodopyrimidin-4-yl)urea**

Intermediate 26 was prepared by an analogous method to Example 24 except by using Intermediate 4 and Intermediate 25. Purification was by flash chromatography on silica using 0-10% MeOH in DCM as the eluent.

MS m/e MH^+ 388.

Example 86

N'-{3-[(2-aminopyrimidin-5-yl)ethynyl]phenyl}-N-(5-tert-butylisoxazol-3-yl)-N-methylurea

Example 86 was prepared by an analogous method to Example 24 by using the compound prepared in Example 23 and Intermediate 28.

^{1}H NMR (DMSO-d_6) 9.48 (s, 1H), 8.43 (s, 2H), 7.73 (s, 1H), 7.49 (d, 1H), 7.33 (t, 1H), 7.17 (d, 1H), 6.54 (s, 1H), 5.39 (br s, 3H), 3.37 (s, 3H), 1.30 (s, 9H);

MS m/e MH^+ 391.

Intermediate 27

5-*tert*-butylisoxazol-3-ylformamide

A solution of *p*-nitrophenyl formate (19.0 g) and 5-*tert*-butylisoxazol-3-amine (14.0 g) in MeCN (100 mL) was stirred at ambient temperature for 16 hours. Aqueous sodium hydrogen carbonate solution (50% saturated, 100 mL) was added and the mixture extracted into DCM. The combined organics were washed with 50% saturated sodium carbonate solution then water and concentrated *in vacuo* to give the title compound as a colourless solid (16.3 g);

^{1}H NMR (DMSO-d_6, major rotamer) 11.07 (s, br, 1H), 8.27 (s, 1H), 6.56 (s, 1H), 1.28 (s, 9H);

MS m/e MH^+ 169.

Intermediate 28

5-*tert*-Butyl-*N*-methylisoxazol-3-amine

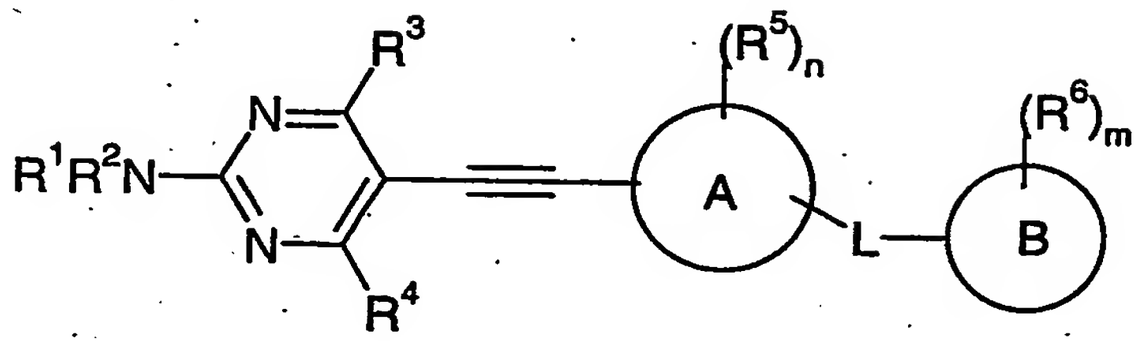
A solution of lithium aluminium hydride in THF (2.0M, 35.4 mL) was added over 40 minutes to a solution of 5-*tert*-butylisoxazol-3-ylformamide (Intermediate 27) (11.9 g) in THF (100 mL) at 0°C. The reaction mixture was warmed to ambient temperature and stirred for 30 minutes. Water (2.7 mL), 2N sodium hydroxide solution (2.7 mL) and water (8.1 mL) were added. The reaction mixture was filtered, the filter cake washed with THF and the filtrate concentrated *in vacuo*. Purification by flash chromatography on silica (35-50% EtOAc in isohexane) gave the title compound as a colourless oil (3.60 g);

^{1}H NMR ($CDCl_3$) 5.44 (s, 1H), 3.77 (s, br, 1H), 2.89 (d, 3H), 1.29 (s, 3H);

MS m/e MH^+ 155.

CLAIMS

1. A compound of the Formula I:



Formula I

wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6, or a 5 or 6 membered heteroaryl ring, or **R^1 and R^2** together with the nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the (1-6C)alkyl, the (1-6C)alkanoyl and the (3-6C)cycloalkyl groups are optionally substituted by one or more groups independently selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl or an alkanoylamino group $-N(R^d)CO$(1-6C)alkyl in which R^d is hydrogen or (1-6C)alkyl, or a saturated or partially saturated 3 to 7 membered heterocyclic ring, or a 5 or 6 membered heteroaryl ring, wherein the (1-6C)alkoxy, (1-6C)alkoxy(1-6C)alkoxy and (1-6C)alkoxy(1-6C)alkoxy(1-6C)alkoxy groups and the (1-6C)alkyl groups of the mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, mono(1-6C)alkylcarbamoyl, di-[(1-6C)alkyl]carbamoyl and/or alkanoylamino groups are optionally substituted by one or more hydroxy groups;

wherein the phenyl is optionally substituted by one or more groups independently selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

and wherein any heterocyclic and heteroaryl rings within R^1 and/or R^2 are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, (1-

4C)alkoxy(1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or $-C(O)(CH_2)_zY$ wherein z is 0, 1, 2 or 3 and Y is selected from hydrogen, hydroxy, (1-4C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and provided that when R^1 and/or R^2 is a (1C)alkanoyl group, then the (1C)alkanoyl is not substituted by fluoro or hydroxy;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy,

wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from: fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, mono(1-6C)alkylcarbamoyl or di-[(1-6C)alkyl]carbamoyl, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, (1-4C)alkoxy, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of R^3 and R^4 is as defined above and the other represents a group $-NR^1R^2$ as defined above;

A represents an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^5 is selected from cyclopropyl, cyano, halo, (1-6C)alkoxy or (1-6C)alkyl, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L is attached meta or para on ring A with respect to the point of attachment of the ethynyl group and represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$, $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or

–O-(CO)-NR^9, wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring, an aryl group, a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl, or a 8, 9 or 10 membered bicyclic group which optionally contains 1, 2, 3 or 4 heteroatoms independently selected from N, O and S and which is saturated, partially saturated or aromatic;

R^6 is selected from halo, cyano, a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -$N(R^c)$CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or

R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the (1-6C)alkyl and the (1-6C)alkoxy groups are optionally substituted by one or more groups independently selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, a (3-7C)cycloalkyl ring or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3;

and when B is a (3-7C)cycloalkyl ring, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a saturated or partially saturated 8, 9 or 10 membered bicyclic group, the rings and the bicyclic group optionally bear 1 or 2 oxo or thioxo substituents;
and pharmaceutically acceptable salts thereof.

2. A compound of the Formula I according to claim 1, wherein:

R^1 and R^2 are independently selected from hydrogen, (1-6C)alkylsulfonyl, phenyl$(CH_2)_u$- wherein u is 0, 1, 2, 3, 4, 5 or 6, (1-6C)alkanoyl, (1-6C)alkyl, (1-6C)alkoxycarbonyl, or (3-6C)cycloalkyl$(CH_2)_x$- in which x is 0, 1, 2, 3, 4, 5 or 6 or **R^1 and R^2** together with the

nitrogen atom to which they are attached represent a saturated or partially saturated 3 to 7 membered heterocyclic ring optionally containing another hetero atom selected from N or O;

wherein the alkyl and the cycloalkyl groups are optionally substituted by one or more groups selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

and wherein the phenyl is optionally substituted by one or more groups selected from halo, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, wherein the (1-6C)alkyl or (1-6C)alkoxy are optionally substituted by hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl or (1-6C)alkoxy wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups selected from fluoro, hydroxy, (1-6C)alkyl, (1-6C)alkoxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino, a saturated or partially saturated 3 to 7 membered heterocyclic ring or a 5 or 6 membered heteroaryl ring, wherein said heterocyclic and heteroaryl rings are optionally independently substituted by one or more of the following: (1-4C)alkyl, hydroxy, amino, mono(1-6C)alkylamino or di-[(1-6C)alkyl]amino or a saturated or partially saturated 3 to 7 membered heterocyclic ring;

or one of R^3 and R^4 is as defined above and the other represents a group $-NR^1R^2$ as defined above;

A represents an aryl group or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^5 is selected from cyano, halo, (1-6C)alkoxy or (1-6C)alkyl optionally substituted by cyano or by one or more fluoro;

n is 0, 1, 2 or 3;

L is attached meta or para on ring A with respect to the point of attachment of the ethynyl group and represents $C(R^aR^b)CON(R^9)$, $N(R^8)COC(R^aR^b)$., $N(R^8)CON(R^9)$, $N(R^8)C(O)$-O-, or –O-(CO)- NR^9 wherein R^8 and R^9 independently represent H or (1-6C)alkyl and wherein R^a and R^b independently represent H or (1-6C)alkyl or R^a and R^b together with the carbon atom to which they are attached represent (3-6C)cycloalkyl;

B represents a (3-7C)cycloalkyl ring, an aryl or a 5 or 6 membered heteroaryl ring selected from furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl;

R^6 is selected from halo, cyano, a saturated or partially saturated 3 to 7 membered heterocyclic ring or an alkanoylamino group -$N(R^c)$CO(1-6C)alkyl in which R^c is H or (1-6C)alkyl; or R^6 is selected from (1-6C)alkyl or (1-6C)alkoxy, wherein the alkyl and the alkoxy groups are optionally substituted by one or more groups selected from cyano, fluoro, hydroxy, (1-6C)alkoxy, amino, mono(1-6C)alkylamino, di-[(1-6C)alkyl]amino, or a saturated or partially saturated 3 to 7 membered heterocyclic ring; and

m is 0, 1, 2 or 3; and when m is at least 2 then two substituents on adjacent carbon atoms in ring B may together represent a methylenedioxy group;
and pharmaceutically acceptable salts thereof.

3. A pharmaceutical composition which comprises a compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in claim 1 or claim 2 in association with a pharmaceutically acceptable diluent or carrier.

4. A compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in claim 1 or claim 2, for use as a medicament.

5. Use of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in claim 1 or claim 2, in the manufacture of a medicament for use as a Tie2 receptor tyrosine kinase inhibitor in a warm-blooded animal such as man.

6. Use of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, as defined in claim 1 or claim 2, in the manufacture of a medicament for use in the production of an anti-angiogenic effect in a warm-blooded animal such as man.

Abstract

A compound of the Formula I.